20th Annual Meeting, American College of Chest Physicians
San Francisco, California, June 17 - 20, 1954

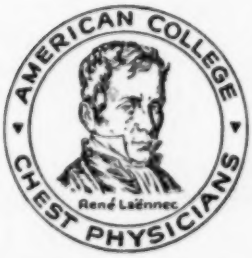
VOLUME XXV NUMBER 4

DISEASES

of the

CHEST

OFFICIAL PUBLICATION



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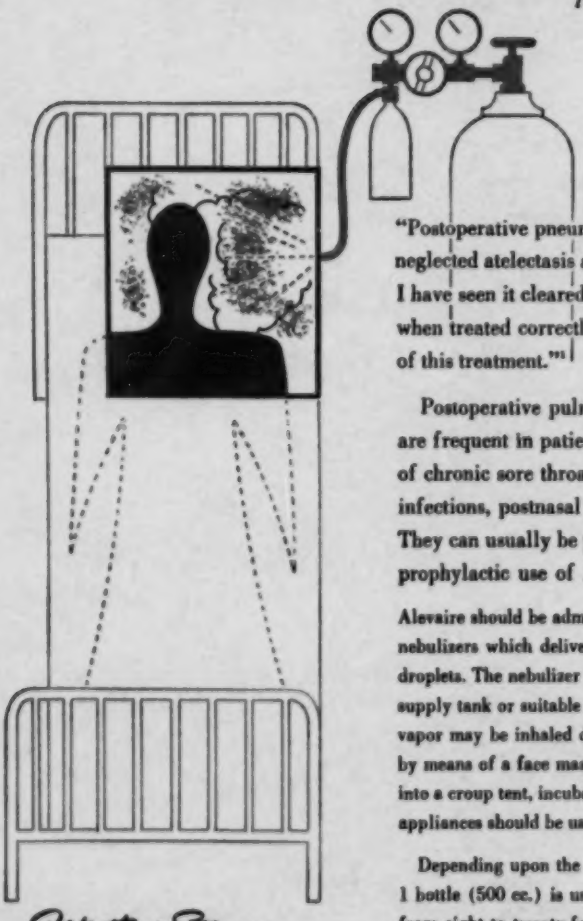

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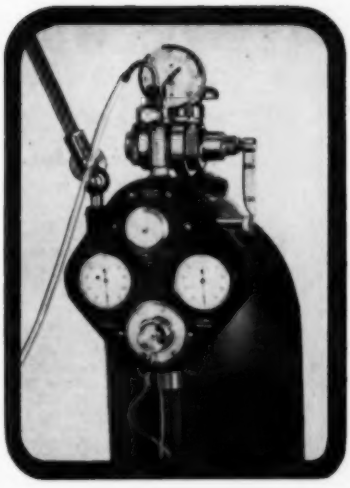

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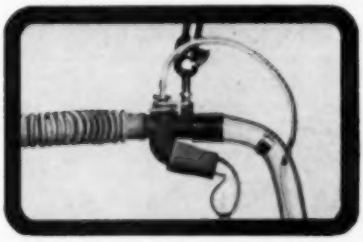

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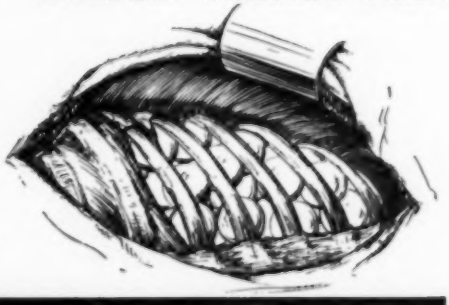

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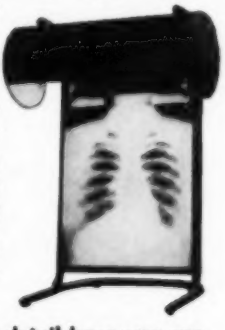

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1. Hobby, G. L., Lenert, T. F., Rivoire, Z. C., Donikian, M., and Pikula, D.: Am. Rev. Tuberc. 67:808, 1953.

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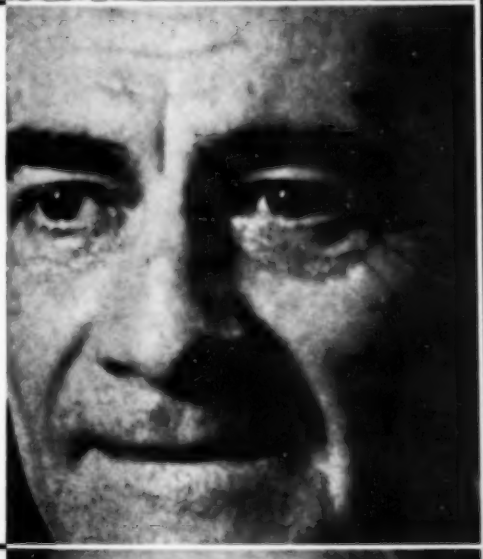

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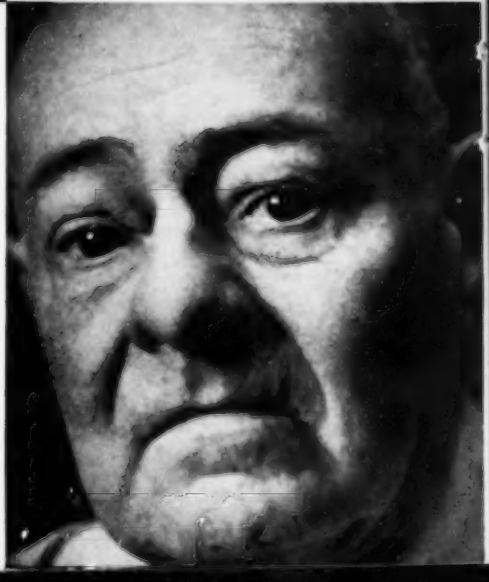

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*English, A. R., et al.:
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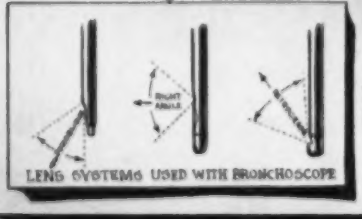

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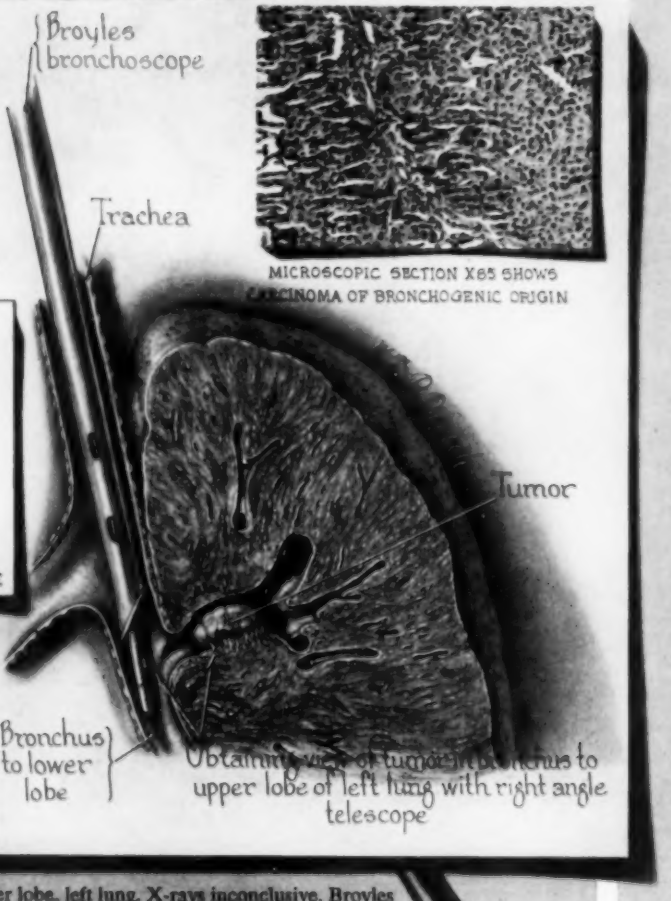
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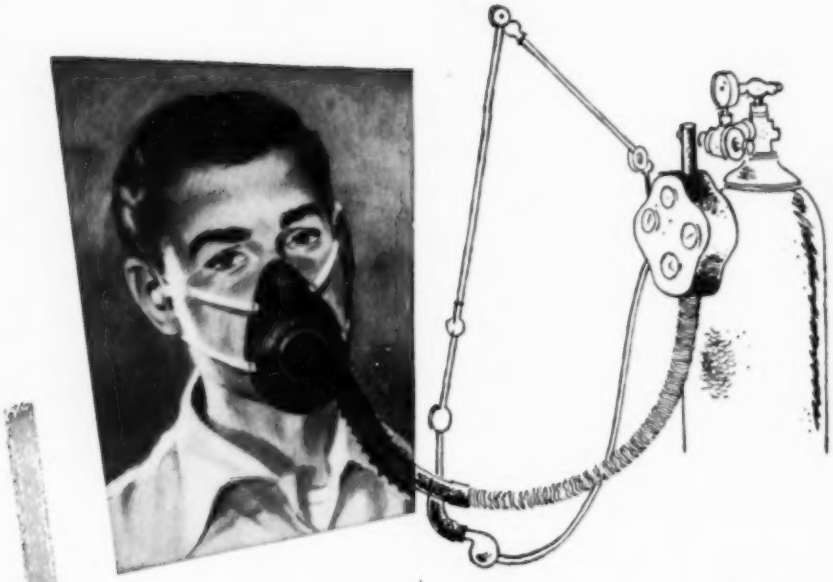

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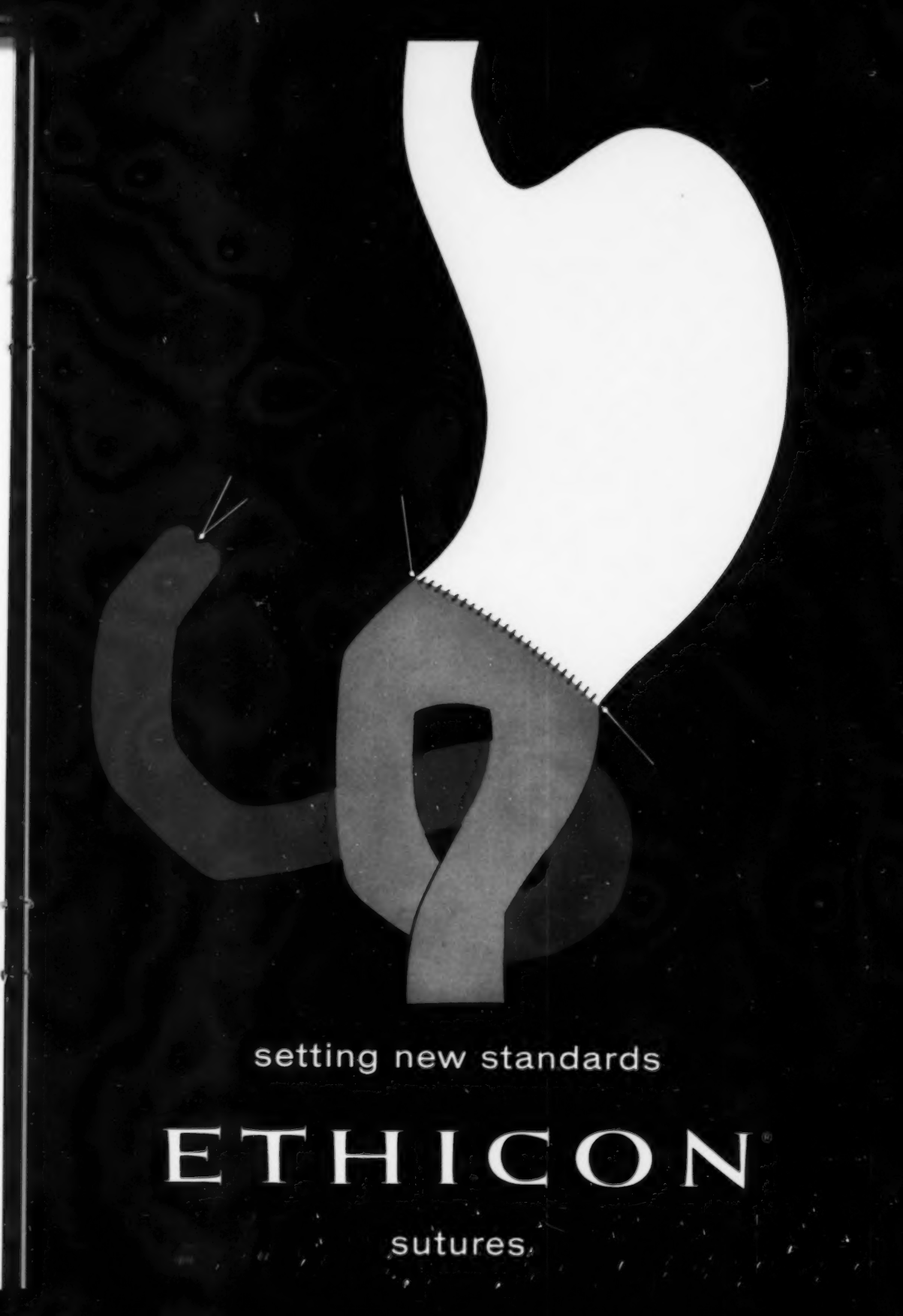
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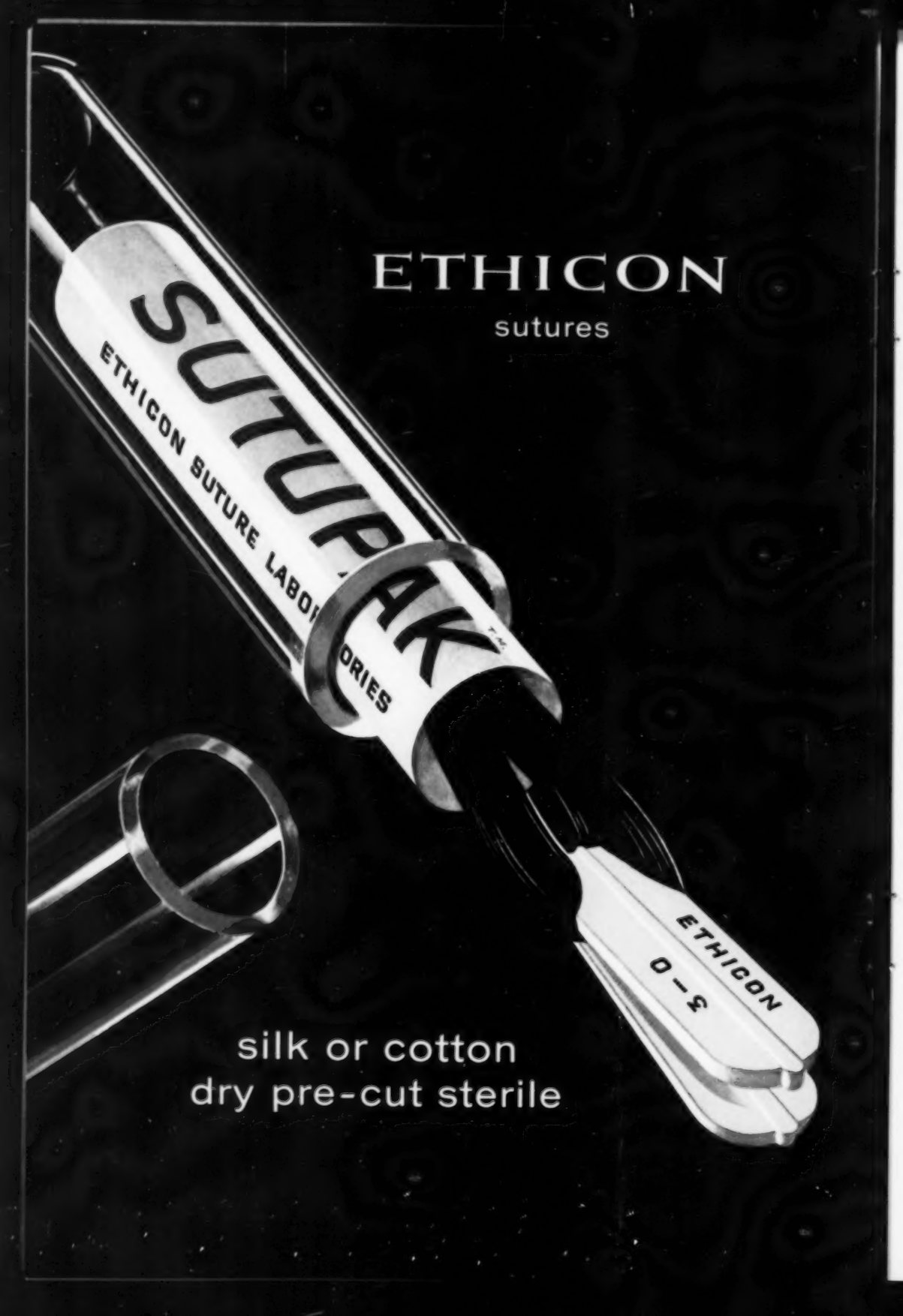
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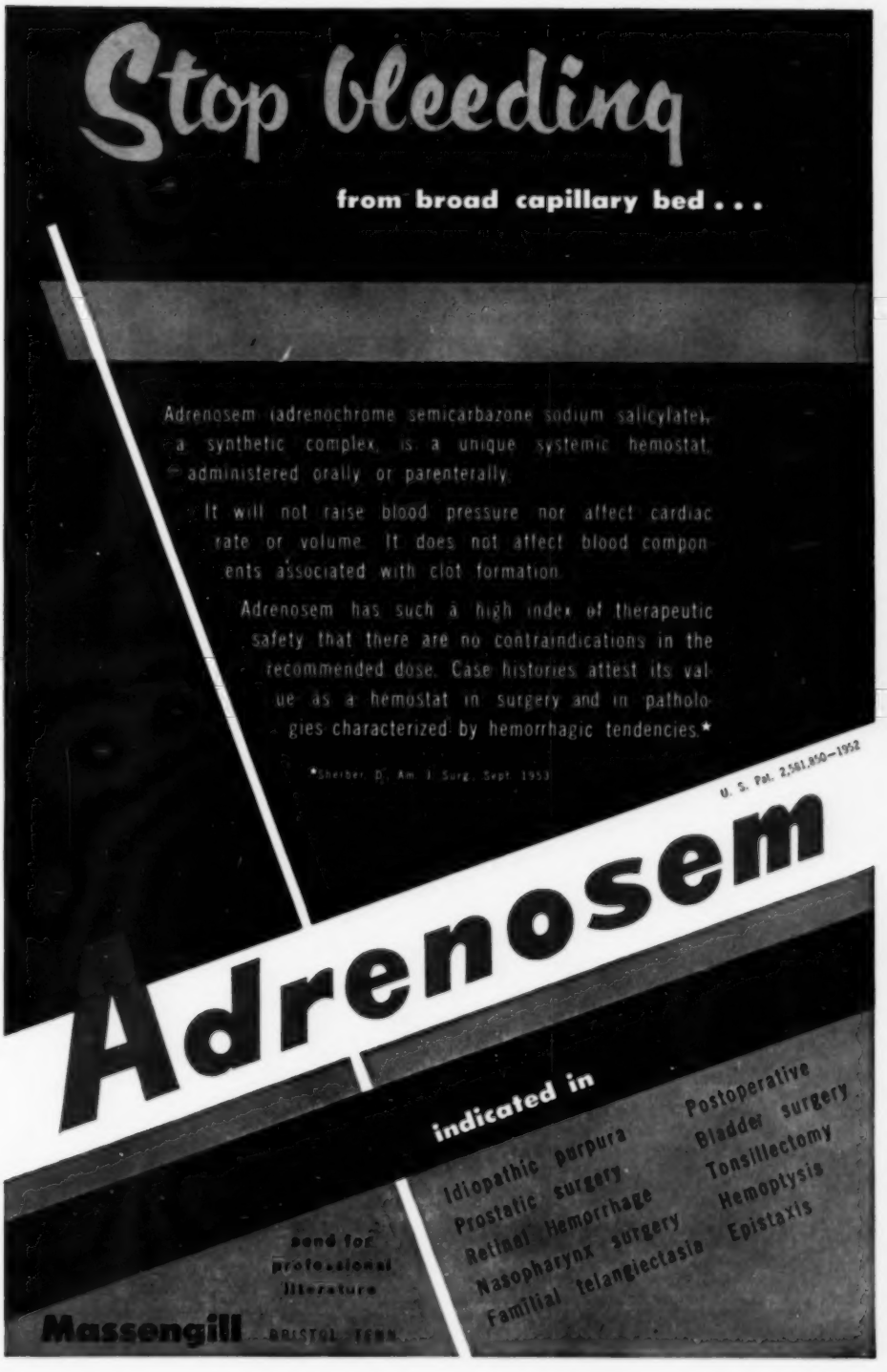
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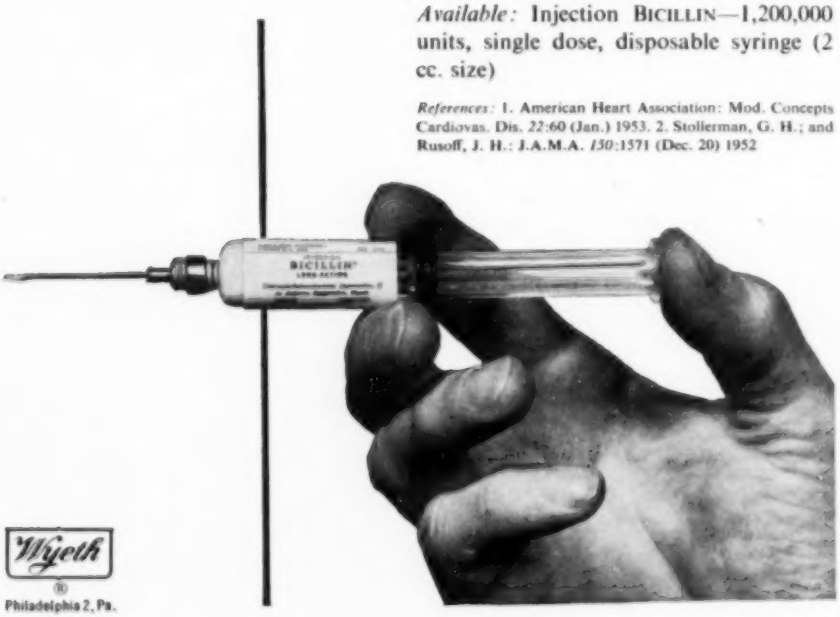

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The Current Treatment of Pulmonary Tuberculosis

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The treatment of pulmonary tuberculosis is a fast changing picture. It is not that what we thought and did yesterday was wrong but what we think and do today is better. The old reliable methods of yesterday, like an old hat or an old automibile, have served their time and been replaced by something better, we hope! Largely due to chemotherapy and advances in surgery all this has come about with dramatic rapidity. I think it was John Hunter (1728-1793), the famous Scotch surgeon, who said: "Don't ask me what I said yesterday! Ask me what I think today!" In discarding the old in our breathless search after something new and better, we must be sure that *discard* and not *renovation* of the old method is right.

At the moment, then, six major trends in the treatment of tuberculosis are evident: the first, toward including early and minimal tuberculosis in schedules of chemotherapy; second, toward greater freedom of activity, less rigid bed-rest for patients without constitutional symptoms while under the protection of chemotherapy; the third, toward greater recognition of the value of the tuberculin test in identifying the date of conversion from negative to positive and therefore, the date of infection; the fourth, away from temporary reversible collapse procedures (pneumothorax, pneumoperitoneum and phrenic operations); the fifth, away from surgical procedures which may reduce pulmonary function (thoracoplasty); and the sixth, toward excision of residual caseo-necrotic lesions.

Discussion of treatment will be divided into two parts with emphasis especially and largely on the inclusion of early tuberculosis in schedules of chemotherapy.

I. *Treatment of Early Minimal Tuberculosis.*

It seems completely illogical not to treat an infectious disease at the earliest possible moment. In May 1951, at the 47th Annual Meeting of the National Tuberculosis Association in Cincinnati, I pleaded[1] for the use of chemotherapy in minimal tuberculosis for the following reasons:

1) Within one hour after subcutaneous inoculation in the experimental animal, virulent tubercle bacilli are widely disseminated throughout the body. (Soltys and Jennings.[2])

2) In experimental tuberculosis in guinea pigs, SM, even though begun

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48 hours before infection, has no influence on the dissemination of the bacilli. It is not until the infected animals treated thus early with SM acquire skin sensitivity to tuberculin that regression in the tuberculous lesion takes place. Tuberculin hypersensitivity and host resistance seem to appear almost simultaneously.[3] Though skin sensitivity to tuberculin and host resistance are not closely parallel phenomena, if the tuberculin test is a fair index of host resistance and it is so used, one need not be afraid that using chemotherapy in a "converter" is starting treatment too early.

3) Streptomycin sensitive and streptomycin resistant tubercle bacilli have the same disease-producing qualities in the experimental animal.

4) No adequate evidence indicates that in a human being a healed lesion containing streptomycin resistant tubercle bacilli will be more likely to break down and become progressive than if the lesion contained sensitive organisms.

5) The fewer tubercle bacilli and the smaller the lesions in the infected animal, the less the probability of the development of resistant bacilli.

To these reasons for the use of chemotherapy in minimal tuberculosis I add the following:

1) It would seem self-evident and all experimental evidence indicates, that, other things being equal, the fewer the bacilli and the smaller the lesions in the infected animal, the more certainly can the disease be controlled by chemotherapy. Early and exudative lesions are more responsive to chemotherapy. Streptomycin does not diffuse readily into large fibrotic and caseo-necrotic lesions. Today residual lesions of this sort are excised. Why not use chemotherapy before these irreversible lesions have time to develop? That number of organisms and number of tubercles alone do not present an insuperable situation is evident from the complete disappearance of miliary tubercles in miliary tuberculosis treated with chemotherapy.

2) Irreversible caseation and necrosis may take place very rapidly in the acute exudative type of lesion.

3) It has been said that the lesions of primary tuberculosis in childhood are unresponsive to chemotherapy, but no adequate evidence has been submitted to show that the basic histologic anatomic lesion, the miliary tubercle, of primary tuberculosis in childhood is any different from the same lesion in so-called reinfection tuberculosis. Large caseating nodes and large caseo-necrotic lesions in the lungs are relatively irreversible lesions at any age of the patient or stage of the disease.

4) The course of tuberculosis in man has been aptly set down by A. Wallgren[4] in his "Time-Table of Tuberculosis" in which he points out that certain of the clinical manifestations of the disease appear at relatively constant intervals after the primary infection. This is one more evidence of the early dissemination of the bacillus. Wallgren, himself, feels that this juncture, the moment of conversion of the tuberculin test and the radiologic recognition of the primary complex, may be the ideal time to start chemotherapy.

5) Barclay[5,6] and others have shown that SM has an immediate effect upon the growth of the tubercle bacillus and large doses cause the death of more bacilli than smaller doses. It is to be emphasized that the bacillus is most vulnerable to both SM and INH during multiplication.

6) The great deterrent of chemotherapy for minimal tuberculosis has been fear of bacterial resistance. This fear was justified in the use of chemotherapy for moderately and far advanced cases of tuberculosis, since surgery, collapse therapy or excision was in the offing and might prove necessary under the protection of chemotherapy. But, for minimal cases, surgery was not contemplated, was beyond the horizon; indeed, timely chemotherapy by preventing the development of irreversible lesions would remove the necessity for surgery. Further, new schedules of chemotherapy, reduction of SM dosage and combinations of drugs have reduced greatly the incidence of toxicity as well as resistance. Admittedly, the correlation of clinical deterioration with the emergence of resistance to SM justified reasonable effort to maintain bacterial sensitivity.

With isoniazid the significance of resistance is different. Middlebrook[7] (1952) has shown that little resistance develops to either drug when SM and INH in therapeutic combinations are added to cultures of tubercle bacilli. Resistance to SM rarely is associated with cross-resistance to INH but resistance to INH has been seen to develop 1,000 times as rapidly as resistance to SM. Resistance to INH does not develop in the absence of ulcerating lesions. Resistance to INH does not develop in closed lesions. Whether the INH resistant tubercle bacillus has lost its pathogenicity is a debatable matter of the greatest importance and cannot be gone into here. It is highly significant that so far meningitis has not been seen in any patient with miliary tuberculosis treated with INH. Also, no patient with miliary tuberculosis treated with INH has relapsed. Edith Lincoln tells me that apparently no physician here or abroad has seen meningitis develop in any patient under treatment with isoniazid. Isoniazid does not act unless organisms are multiplying nor does resistance develop. For all these reasons it seems imperative that tuberculosis should be treated at the earliest possible moment of recognition.

How promptly, how early can one diagnose tuberculous infection? As soon as the tuberculin test is converted from negative to positive! If pediatricians would use the tuberculin test more frequently, not only on children in the homes of tuberculous families but on all children, tuberculosis would be diagnosed more often, more early. The use of the tuberculin test in highly exposed adult groups, such as medical students, student and graduate nurses and all hospital personnel should be obligatory. The tuberculin test serves two important functions; properly used it tells us not only that infection has taken place but *when*, and perhaps even *where* that infection occurred. The latter has long been appreciated in Scandinavian countries but too long forgotten or disregarded in this country. ***Now that we have potent, inexpensive and easily taken antibiotics against the tubercle bacillus, every effort should be made to identify the moment of infection, the time of conversion of the tuberculin test, so that treat-***

ment may be started. Obviously, if the time of conversion of the tuberculin test is to be used to start treatment in recent converters, BCG vaccination of these highly exposed persons must be discarded. A decision on this important matter is inescapable, either "vaccinate and prevent" or "tuberculin test and treat recent converters".

Yesterday, it was said 90 odd per cent of persons with minimal tuberculosis will get well anyhow on bed-rest alone, therefore, chemotherapy should be kept in reserve until things go bad. This doctrine of complacency is all wrong. I view with alarm the immediate as well as the remote future of the person with minimal tuberculosis! As soon as active tuberculosis lifts its head, I believe in taking a crack at it. The following observations (they can be multiplied) illustrate the importance of the time of conversion of the tuberculin test in relation to the appearance of clinical tuberculosis.

Bewley[8] (1950) found symptoms of tuberculosis among 22 of 50 Irish nurses converting their tuberculin test. Subsequent signs and symptoms of active disease developed in six of the nurses (three plueral effusions, two pulmonary infiltrations, one "phthisis" successfully treated with artificial pneumothorax). Brun and Plauchu[9] (1947) in a four to 11 year follow-up study of student nurses in Lyons, found that 92 of 116 originally Pirquet negative converted during training, which did not include service in tuberculosis wards. Three nurses died early, two of meningitis and one of miliary tuberculosis. In addition, two other nurses developed pleural effusion and seven pulmonary tuberculosis. It is also important that the fatal cases were not those with the most severe initial reactions!

Bates and Davey[10] at the University of Michigan, after 10 years' observation on student nurses and three years' observation on medical students, say "all cases of tuberculosis appeared in students negative to tuberculin on entrance to school." Dr. Helen Dickie[11] at the Uneversity of Wisconsin, in a study of medical students graduating from 1934 through 1943, says: "Of 188 students originally tuberculin negative, 19 or 10.1 per cent developed tuberculosis; of 95 originally positive, two or 2.1 per cent developed tuberculosis; of 138 "converters," 19 or 13.7 per cent developed tuberculosis."

Dr. Edith Lincoln[12] in a most valuable study of the course and progression of first infection tuberculosis in the child says three factors influence the prognosis: the age of the child when infected, the duration of the primary tuberculosis, and "to a lesser degree the extent of the tuberculous process." To my mind, it follows with irresistible logic, the *younger* the child, the *shorter* the duration of the infection, the *less* the extent of lesion, the more urgent the need of chemotherapy. More than half of the infants first diagnosed under six months of age died of tuberculosis, 28 per cent of those between one and two years when first diagnosed died of the disease, and 14 per cent of those diagnosed when five through nine years of age.

As to the age of the lesion, 90 per cent of the deaths occurred within a year of the first diagnosis of primary tuberculosis, 75 per cent within six months and 60 per cent within three months.

Since obstructive lesions in children from enlarged nodes encroaching

on the bronchi are difficult to distinguish radiologically from parenchymal lesions, the size of the primary complex is difficult to estimate. At any rate the mortality rate in children with the largest lesions was more than double the rate in children with small primary foci.

One must not conclude from this that the infant is "devoid of resistance." Of 470 children infected with tuberculosis during the first year of life, 395 or 84 per cent were alive and well four to seven years later. (Bernard et al.,[13] 1925; Myers and Kernkamp,[14] 1930; Asserson,[15] 1927; Brailey,[16] 1936). However, it is generally agreed that the native resistance of the infant is less than that of the older child and the adult. Furthermore, we need to know how many of these children escape clinical disease in childhood only to succumb in later life!

At the National Jewish Hospital a project has been underway for three years in which cases of uncomplicated pulmonary tuberculosis in childhood have been alternated—half of them have received chemotherapy, the other half no chemotherapy. The doctors in charge of this project do not believe that they yet have clear-cut statistical evidence that all cases of childhood tuberculosis should be treated with antibiotic agents but their results thus far are consistent with my personal opinion that all cases of early, "uncomplicated" as well as "progressive" tuberculosis in children should receive the benefits of early chemotherapy.

Although my main theme is advocacy of early diagnosis of the most minimal lesions and prompt chemotherapy, I agree that the most important method of protecting the infant is removal of the source of infection from the household. As to the remote future, Mitchell[17] found that modified bed-rest alone, as used at the Trudeau Sanatorium during the years 1927 through 1946, failed in 27.6 per cent of 589 patients with active uncomplicated minimal pulmonary tuberculosis to prevent progression to advanced disease during a 20 year follow-up period for the entire group. Although the mortality from tuberculosis was only 5 per cent in 20 years, "progressions and recurrent progressions of minimal tuberculosis produced a total loss of economic usefulness of sufficient magnitude to justify a continued search for a more dependable form of treatment for minimal tuberculosis than modified bed rest." To this concluding statement of Mitchell I would add that relapse is not just a matter of personal, of individual concern. Every relapse adds one more to the list of persons with a communicable disease.

Let us now proceed to a discussion of early tuberculosis as it is found under certain specific clinical conditions.

a) *Accidental skin inoculation tuberculosis.* A young technician accidentally sticks a finger with a needle attached to a syringe loaded with virulent tubercle bacilli and develops a tubercle at the site of inoculation. A butcher ("butcher's tubercle"), a pathologist ("post-mortem tubercle"), or a surgeon may suffer the same accident. A well-proved tuberculous ulcer develops. What to do about this? So far as treatment is concerned it makes no difference whether this person, male or female, had a prior positive tuberculin test. Chemotherapy should be given promptly and continued at least six months. Granted that the "butcher's tubercle," an infection with

the bovine bacillus and the "post-mortem tubercle," an infection with the human bacillus, are both, in the vast majority of circumstances, localized and non-progressive lesions, nevertheless, they are not always so. Grady[18] (1951) reviews the literature and reports eight cases in five of which the local lesion and its associated regional nodes caused serious illness. These unpredictable lesions always should be treated with chemotherapy in the hope that excision of indolent ulcers and suppurating or caseous regional lymph nodes will not be necessary.

b) *The recent "converter" with minimal lesion demonstrated by x-ray film and positive gastric washings and/or sputum.* In 1951 the majority opinion held that these patients would get well anyhow and antibiotics should be kept in reserve in case surgery would ultimately prove necessary. Today, I think it is generally accepted that modified bed-rest and chemotherapy is the right thing.

c) *The recent "converter" with or without positive gastric washings and/or sputum but without lesions being demonstrated on the x-ray films.* To treat these persons with chemotherapy is to attack the disease at its most vulnerable point. This is the Achilles heel of tuberculous disease! These persons should be treated with chemotherapy because: (1) The x-ray film cannot reveal all parts of the lungs. The bony thorax and its soft parts, the shoulder girdle and spine and their associated muscles hide from view some 20 to 30 per cent of the lung fields; (2) In the adult especially, tuberculosis is almost always inhalation infection. The primary focus therefore, must be in the lungs but because it cannot be seen some illogically decline to treat it with chemotherapy. I make this recommendation despite the fact that I believe the person without a "visible primary lesion" is less severely threatened than the "converter" with a "visible primary lesion." Of 45 nurses recorded in the Prophit Survey[19] with "visible primary lesions," 20 developed clinical tuberculosis, while of 545 without a "visible primary lesion" only 28 subsequently showed evidence of disease. However, it would be more safe to treat with chemotherapy these persons, infants, young children, adolescents and young adults, converting their tuberculin tests under observation until adequate experience is acquired to tell us whether we have or have not reduced the hazard of later active clinical disease.

d) *The symptom-free converter of undetermined date with positive sputum and/or gastric washings and positive x-ray film.* Today all agree that this person should receive chemotherapy.

e) *The symptom-free converter of undetermined date with negative sputum and/or gastric washings and negative x-ray film.* A lucky guy! At this time, he has nothing to worry about!

II. *Treatment of Late Tuberculosis.*

The trend is toward excision of caseo-necrotic lesions, so-called "irreversible" or "residual" lesions, those remaining after what seems at the moment, adequate chemotherapy, meaning by "adequate" wise choice of drugs in combination, proper daily dosage and duration of treatment. Tuberculosis is notoriously prone to relapse. In the past the responsibilities

of the physician toward the tuberculous person under his care were in the main three-fold: (1) to help his patient to get well, (2) to teach him to avoid errors of work and play that might lead to relapse, (3) to teach him enough about the communicability of the disease that he would not infect family contacts or anybody else. Today, the physician has the same responsibilities, but whereas formerly the responsibility to avoid relapse was largely placed on the shoulders of the patient, today, by chemotherapy the doctor actively helps to prevent relapse by preventing the development of irreversible lesions; and, by excision of "residual" lesions the surgeon attempts to remove the most important cause of relapse. At the moment, we are confident that excisional surgery is a wise and successful procedure *in properly selected cases*. The difficulty is when to excise and when to leave well-enough alone! Without doubt some lesions are being excised which never would cause trouble again. I call these Last Year's Bird Nests (LYBN's). It is not possible, of course, to remove all diseased tissue, one can remove only the most menacing lesion or lesions, and these are often cavitary, closed or open.

In some hospitals, anxiety to speed decision on this vital matter is so great that "time-honored" collapse measures both temporary (pnx., pnp. and phrenic operations) and permanent (thoracoplasty) have been completely laid aside. Time will give the answer to this and other problems of treatment. One must have patience. It is greatly to the credit of the medical profession that this search after truth, after the best way to treat the tuberculous patient is proceeding discreetly, advisedly though enthusiastically, and conservatively though searchingly with the good of the patient never lost to mind.

General Comment on Chemotherapy in Tuberculosis

H. Florey[20] (1952) describes the ideal chemotherapeutic agent as follows: It should be non-toxic in therapeutic effective doses, preferably bactericidal rather than bacteriostatic, reach high concentrations in the blood after either oral or parenteral administration, perfuse readily into serous cavities and penetrate caseous foci in effective concentrations. It should diffuse into macrophages and epithelioid cells, that is be effective against intracellular tubercle bacilli as well as extra-cellular bacilli. It should not be carcinogenic or antigenic nor should it easily promote bacterial resistance. It should be of large molecular size so that it will pass out of abnormally permeable blood vessels in areas of inflammation and remain to reach a relatively high concentration in the infected area. All of the four most popular drugs are toxic, but fortunately therapeutically effective dosage schedules have been found which have greatly minimized this danger. Isoniazid seems less toxic for children and monkeys than for adults. The clinical significance of this is not yet fully apparent. "Peripheral neuritis" is being recorded with disturbing frequency in adults treated with isoniazid. More allergic reactions occur from SM than DHSM. Streptomycin may damage the vestibular branch of the eighth nerve and DHSM the auditory branch. Preparations now on the market of equal parts SM and DHSM

(Duo-Strep, Combistrep, and Distrycin) may have successfully solved this problem. Sensitivity to SM does not always mean sensitivity to DHSM. These effects are central rather than peripheral. Both SM and DHSM have bactericidal but mainly bacteriostatic actions. The concentration of SM required to inhibit the intracellular growth of tubercle bacilli is about 100 times greater than that required to control extracellular growth. On the other hand, isonicotinic acid hydrazide is as effective against intracellular bacilli as against extracellular bacilli. PAS is almost wholly inactive against intracellular bacilli. Streptomycin and DHSM do not diffuse readily into caseo-necrotic lesions. As to resistance, present schedules of SM and DHSM combined with other drugs have gone a long way to delay the emergence of resistance.

Mackaness and Smith[21] from in vitro studies concluded that SM and isoniazid have comparable bactericidal qualities in low concentrations. Barclay and associates using radioactive INH say the initial action of INH is bacteriostatic and may be by interference with formation of an essential metabolite. Both in vitro and in vivo studies on the combined use of INH and SM show that a synergistic effect occurs only when effective, and not when subeffective doses are given. Also this combination does not entirely prevent the emergence of resistance and cross resistance may occur. Barclay also has shown that after intramuscular injection the highest concentrations of INH were found in the lungs and the skin and that diffusion into dense caseo-fibrotic lesions in lungs and lymph nodes readily took place.

Modified Bed-rest Regime

During the early stages of active pulmonary tuberculosis the patient is often highly sensitive to "auto-inoculation of tuberculin". At this time rigid bed-rest remarkably controls fever, quiets the pulse, reduces cough and expectoration, improves the appetite, dissipates malaise and restores badly shaken morale. Disregard of rest often leads to aggravation of symptoms and spread of disease. Unfortunately, prolonged bed-rest too often leads to uncontrolled boredom, restlessness ending in recklessness (A.M.A., A.W.O.L. and the like) and disaster. Some patients just can't take it. Bed-rest is good medicine but like every other good medicine has its optimum dosage. In too large doses it is a destroyer of morale, an instigator of rebellion, and defeats its purpose. In too small doses, it is wellnigh worthless. If chemotherapy will make it possible to treat tuberculosis on a modified ambulatory basis, it will be a God-send! By "modified ambulatory basis" I do not mean permission to go home without strict supervision! I do not mean approval to prowl the streets. The public health aspects of ambulatory treatment are perhaps more important than the health of the individual patient.

I have said that bed-rest remarkably controls fever. Chemotherapy also remarkably reduces fever and other "toxic" symptoms. Today it is amazing to see how little fever is recorded on the hospital charts of tuberculous patients taking chemotherapy. I conclude that under the protection of

chemotherapy the formerly very rigid regimens of bed-rest may be relaxed for some cases and the patient started more early on graduated exercise but every case must be individualized. No patient with positive sputum should be treated on an ambulatory basis.

At the moment, the four most valuable drugs are SM, DHSM, PAS and INH. PAS has bacteriostatic value and in combination with SM helps to delay emergence of resistance. Unfortunately, many patients cannot take it. Viomycin is a valuable drug but more toxic and more expensive. It can replace SM when necessary. Terramycin is also more expensive but may substitute for PAS when that drug cannot be tolerated.

In some quarters, I find a tendency to keep something in therapeutic reserve; to fight with one hand holding a gun behind the back, not to use both SM and INH at the same time. The argument runs, if you use both drugs simultaneously and resistance or sensitivity develops to both, the patient is out of luck. At this time, evidence is lacking that combined SM and INH are superior to combined SM and PAS. In the same breath it is admitted that SM, INH and PAS is the most potent combination and should be used in the treatment of the most serious "complications," tuberculous meningitis. I am congenitally opposed to fighting with one hand behind the back. Minimal tuberculosis means the house is on fire! Call out the fire department! I recommend all three drugs (SM, INH and PAS) for minimal tuberculosis as well as the more serious situations! However, more experience, especially with INH, may prove that in some cases a policy of "therapeutic reserve" is wise.

SUMMARY AND CONCLUSIONS

1) At the moment, six major trends in the treatment of tuberculosis are evident: the first, toward including early and minimal tuberculosis in schedules of chemotherapy; second, toward greater freedom of activity, less rigid bed-rest for patients without constitutional symptoms while under the protection of chemotherapy; the third, toward greater recognition of the value of the tuberculin test in identifying the date of conversion from negative to positive and therefore, the date of infection; the fourth, away from temporary reversible collapse procedures (pneumothorax, pneumoperitoneum and phrenic operations); the fifth, away from surgical procedures which may reduce pulmonary function (thoracoplasty); and the sixth, toward excision of residual caseo-necrotic lesions.

2) Recent tuberculin converters among highly exposed persons, with or without visible primary lesions or radiologic "active minimal tuberculosis" whether children or adults, should be treated with chemotherapy.

3) Accidental skin inoculation tuberculosis should be treated promptly with chemotherapy.

4) Active means to prevent relapse of minimal tuberculosis include timely chemotherapy and excision of residual caseo-necrotic lesions. Further experience is required before final evaluation of these measures.

5) Although present combined schedules which include one gram SM two or three times weekly rarely cause damage to the eighth nerve, the

present commercial preparations of equal parts SM and DHSM are adequately effective and reduce the possibility of toxic effects during or following long continued therapy.

6) Chemotherapy for recent tuberculin converters and persons with minimal tuberculosis should reduce, in some cases, the necessity for prolonged bed-rest.

7) Combined streptomycin, isoniazide and PAS are all recommended for simultaneous use for minimal tuberculosis in adults and the more severe complications of tuberculous disease at any age. Under special circumstances in adults SM or INH, one or the other, may be withheld temporarily, but PAS or terramycin must be given simultaneously. Special regimens are required for the treatment of primary tuberculosis in children.

The tuberculin test serves two important functions: first, it tells whether tuberculous infection has taken place or not; second, by proper repetition of the test especially in children and in all highly exposed persons, it will tell *when* that infection took place and even *where* that infection occurred. Use of the tuberculin test in this way has shown that many of the important clinical manifestations of tuberculosis, both in children and in adults, appear often within a few months if not in a few years after primary infection, that is after conversion of the negative tuberculin test to positive. This makes it possible to start treatment promptly after infection and before disease is well established.

Isoniazid has not yet been fully appraised but both clinical trials and well conducted experiments in animals indicate that besides great value in the treatment of active disease, it may have even more important influence in the prevention of tuberculous disease after infection has taken place. For these reasons, I urge again that chemotherapy, especially including isoniazid, be used not only for the treatment of primary and minimal tuberculosis but also as "preventive therapy" in the treatment of certain recent "converters" of the tuberculin test from negative to positive.

RESUMEN Y CONCLUSION

1) En el momento actual, son evidentes seis tendencias principales en la quimioterapia de la tuberculosis; la primera es: incluir dentro de los planes de quimoterapia la tuberculosis temprana y mínima; la segunda, hacia una mayor libertad de actividad, menos rigidez en el reposo en cama para los enfermos sin síntomas generales mientras están bajo la protección de la quimioterapia; la tercera, tendencia hacia el reconocimiento mayor de la importancia de la reacción tuberculínica para la identificación de la fecha de conversión de negativa a positiva y por tanto, de la fecha de la infección; la cuarta, alejándose de los procedimientos de colapso temporal y reversible (neumotórax, neumoperitoneo, y operaciones del frénico); la quinta, alejándose de los procedimientos quirúrgicos que pueden reducir la función del pulmón (toracoplastía) y la sexta, hacia la excisión de las lesiones residuales caseo-necróticas.

2) Aquellos que viran su reacción, entre los altamente expuestos, con

lesiones primarias visibles o no, o con "tuberculosis mínima activa" va sea niños o adultos, deben ser tratados con quimioterapia.

3) La inoculación accidental con tuberculosis debe ser tratada prontamente con quimioterapia.

4) Los medios activos para prevenir la tuberculosis mínima incluyen oportuna quimioterapia y excisión de lesiones caseo-necróticas. Se requiere ulterior experiencia para una valuación final de estas medidas.

5) Aunque los regímenes terapéuticos combinados que incluyen un gramo de estreptomicina, dos o tres veces por semana, rara vez dañan el octavo par, las preparaciones comerciales actuales con partes iguales de estreptomicina y dihidroestreptomicina son adecuadamente efectivas y reducen la posibilidad de manifestaciones tóxicas durante o después de tratamiento largamente continuado.

6) La quimioterapia para los que han virado recientemente y para las personas con tuberculosis mínima reduciría en algunos casos, la necesidad de reposo en cama.

7) La combinación de estreptomicina, isoniacida, y PAS, son recomendables para uso simultáneo en los adultos y en las más severas complicaciones de la tuberculosis en toda edad.

Bajo circunstancias especiales en los adultos, estreptomicina o isonicotinamida una o la otra, pueden ser retiradas temporalmente, pero PAS o terramicina deben darse simultáneamente.

Regímenes especiales se requieren para el tratamiento de la tuberculosis primaria en los niños.

La prueba tuberculínica sirve para dos importantes funciones: Primera: informa si la infección tuberculosa ha tenido lugar o no; segunda: mediante su adecuada repetición en los niños y en todas las personas altamente expuestas, dice cuando la infección ha tenido lugar y aún, donde ha tenido lugar.

El uso de la reacción tuberculínica de esta manera ha demostrado que muchas de las manifestaciones clínicas de la tuberculosis tanto en los niños como en los adultos aparecen a menudo algunos meses si no es que algunos años después de que la infección primaria se ha verificado o sea después del viraje de la reacción tuberculínica. Esto hace posible el empezar el tratamiento inmediatamente después de la infección y antes de que la enfermedad esté bien establecida.

La isoniacida no ha sido aún completamente valorada pero tanto por el ensayo clínico como por experiencias bien conducidas en animales, han demostrado que además de gran valor en el tratamiento de la enfermedad activa puede tener aún mayor influencia en la prevención de la enfermedad tuberculosa después de verificada la infección. Por estas razones considero urgente otra vez que la quimioterapia incluyendo la isoniacida especialmente, se usen no sólo para el tratamiento de la tuberculosis primaria y mínima de la tuberculosis, sino también el "tratamiento preventivo" de ciertas personas que han virado recientemente de la tuberculino-negatividad a la positividad.

RESUME ET CONCLUSION

1) Au moment présent six tendances majeures sont évidentes dans le traitement de la tuberculose: la première tend à inclure le, tuberculoses précoces et minimes dans le cadre de la chimiotherapie; la second tend à autoriser une plus grande liberté d'activité et à moins condamner au strict repos au lit les malades sans symptomes constitutionels et sous le protection de la chimiotherapie; la troisième tend à affecter une plus grande valeur au test à la tuberculine pour déceler la date de sa conversion de negatif à positif, et ainsi l'époque même de l'infection; la quatrième tend à s'écarter des procédés de compression pulmonaire réversibles (pneumothorax, pneumopéritoine et opérations sur le nerf phrenique); la cinquième tend à s'éloigner des procédés chirurgicaux qui peuvent réduire la fonction pulmonaire (thoracoplastie); et la sixième incite à exciser les reliquats des lesions caséo-nécrotiques.

2) Parmi les personnes exposées et dont la réaction à la tuberculine à viré récement le tratement s'impose par la chimiotherapie et cela qu'ils aient des lésions primaires visibles ou invisibles radiologiquement "tuberculose minime active," qu'il s'agisse d'enfants ou d'adultes.

3) Une inoculation tuberculeuse accidentelle de la peau doit être traitée rapidement par la chimiothérapie.

4) Les moyens actifs de prévenir les rechutes de tuberculose minime comprennent avec la chimiothérapie au bon moment l'excision des lesions nécro-caséeuses. Plus d'expérience est requise avant de pouvoir évaluer définitivement ces mesures.

5) Bien que les programmes combinés qui incluent un gramme de Sm deux ou trois fois par semaine rarement altèrent la huitième paire nerveuse, il faut savoir que les préparations commerciales qui contieunent à parties égales la SM et DHSM sont réellement actives et réduisent la possibilité d'effects toxiques dans le cours d'une thérapeutique longtemps suivie.

6) La chimiotherapie appliquée, aux porteurs de réaction à la tuberculine ayant viré récement ou de tuberculose mínime, devra reduire dans quelques cas, la nécessité d'un repos au lit prolongé.

7) La combinaison streptomycin, isoniazid, et PAS est recommandée en usage simultané pour les cas de tuberculosis minime des adultes, comme pour les complications plus sévères de la maladie tuberculeuse à tout âge. Dans les circonstances spéciales chez l'adulte la SM ou l'IHN, soit l'un soit l'autre, peuvent être supprimes temporairement, mais le PAS et la terramycin doivent etre donnés simultanément. Des régimes spéciaux sont requis pour le traitement de la tuberculose primarie des enfants.

Le test à la tuberculine sert deux fonctions importantes: premièrerement il affirme si oui ou non l'infection tuberculeuse existe; deuxièmemtnt par la répétition de ce test chez l'enfant et chez les personnes exposées, on peut determiner quand et même où cette infection s'est declanchée. L'utilisation de cette mainère du test à la tuberculine à montré que beaucoup des manifestations cliniques importantes de la tuberculose, chez les enfants comme chez les adultes, n'apparaisent souvent que plusieues mois sinon

souvent plusieurs années après le vizage de la réaction à la tuberculine de négative à positive. Ceci permet de commencer un traitement rapidement après l'infection et avant que la maladie ne soit bien installée.

La complète valeur de l'Isoniazid n'a pas encore été complètement évaluée, mais les essais cliniques commes les expériences animales indiquent qu'en dehors de la grande valeur dans le traitement de la maladie active, il se peut qu'elle exerce encore un influence beaucoup plus importante pour la prévention de la maladie tuberculeuse après que l'infection s'est déclarée. Pour ces raisons j'insiste à nouveau pour que la chimiothérapie, surtout comprenent l'isoniazid, soit utilisée non seulement pour le traitement de la tuberculose primaire et minime, mais aussi à titre de "thérapeutique preventive" dans le traitement de certains "virés" recents d'un test à la tuberculine négatif à un test positif.

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The Present Status of Isoniazid in the Treatment of Pulmonary Tuberculosis*

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After the sensational announcement of isoniazid as a remedy for tuberculosis a little over a year ago, it is highly proper at this time to inquire about its present status—to assess its value and to describe its mode of action as much as the known facts will permit. There is no doubt that the first wave of enthusiasm was not entirely justified by subsequent trials in various forms of tuberculosis. It fell considerably short of the ideal chemotherapeutic agent. For example, it is not definitely bacteriocidal and the bacilli soon gain resistance. On the other hand, it has achieved results that are equal to and perhaps superior to streptomycin in certain aspects of treatment of the disease. Combined with other drugs it constitutes a distinct advance in anti-tuberculosis therapy.

There is no point at this late date to go into the historical development of this interesting chemical. The early experiments were reported by several different laboratories and clinics.[1-8] As an organic compound it is a relatively simple one. It was first prepared in 1912 and it lay on the chemists shelf for nearly 40 years before its usefulness in tuberculosis was discovered. As an agent against tuberculosis it may be compared to the keystone of the Arch of the Temple that was by-passed for a long period of time before its true place was found.

It must be pointed out that all of the actions and the exact mechanism of the action of this interesting chemical on the tubercle bacillus and on the human body, is by no means completely solved. There seems to be little question that there is a stimulating effect upon the body that is not possessed by any other anti-tuberculosis agent although streptomycin does create some feeling of well being due perhaps to the cutting off of toxins caused by the disease. There seems to be, on the part of isoniazid, a direct cerebral stimulation over and above that on the disease thus causing a feeling of well being and a stimulation of appetite. It may be due to the fact that the niacin fraction of the isoniazid may possess an action on the body over and above that produced by the action on the tubercle bacillus.

The action on the tubercle bacillus itself has been studied by various workers with the result that much has been learned concerning the mech-

*From the State of Florida Tuberculosis Hospital System.
The Isoniazid for these experiments was furnished by:
1) Pfizer & Co., Brooklyn, N. Y. Courtesy of Dr. Gladys Hobby.
2) Parke-Davis & Co., Detroit, Mich. Courtesy of Dr. C. M. Sharp.
3) Squibb & Co., New York City. Courtesy of Dr. Geoffrey Rake.
We extend our thanks to each of these firms and individuals for their generosity.

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anism of the action on the tubercle bacillus, both in vitro and in vivo. One of the most interesting and important studies was carried out by Barkley, Ebert and Koch-Weser.[9] The growth curves of tubercle bacilli recorded by these authors in Dubos-Davis Medium revealed the fact that isoniazid was not bacteriocidal. Growth did not stop immediately when the bacilli came in contact with isoniazid but continued on for at least another generation. This indicated to these authors that isoniazid interfered with some vital metabolite rather than causing any abrupt cessation of growth activity. After the drug is added there is enough of the metabolite present in the bacilli to continue on for another cell division before activity stopped. Indeed they suggested that the isoniazid may have entered into the formation of a combination with some vital enzyme and diverted it from its action. This result was different from that obtained with streptomycin where there was an abrupt cessation of growth activity as soon as the bacilli came in contact with the drug. Furthermore, there was a liquefaction of many bacteria exposed to streptomycin showing that there was a considerable bacteriocidal action. This effect was not produced at all by isoniazid.

These same authors developed an ingenious method of testing the effect of isoniazid on the resistant and non-resistant strains of tubercle bacilli. They caused to be made in the chemical laboratory a radio active isoniazid by incorporating "carbon 14" in the carboxyl position of the isoniazid molecule. The experiments revealed that sensitive bacilli took up the compound in large quantities whereas the resistant strains took up practically none.

Steenken and Wolinsky[10] were able to heal experimental lesions in rabbits by intensive isoniazid treatment so that no growth or infections could be produced from the lesions. The explanations could be that the rabbits were infected entirely with bacilli undergoing active cell division.

Of great interest also is the work of Mackaness and Smith[11] on the extracellular and intracellular tubercle bacilli treated by various antituberculosis agents including isoniazid, streptomycin and terramycin. These authors found that isoniazid perhaps due to its small molecule penetrated specially prepared macrophage cells containing tubercle bacilli and prevented growth activity of the bacilli within these cells. This action was almost equal to that obtained by isoniazid in extracellular fluids. Streptomycin did not have intracellular activity except in high concentrations. These observations are most important and perhaps help to explain much of the favorable effect of isoniazid in miliary tuberculosis and tuberculous meningitis where the penetration of cells is important. For the same reason it may be that the smaller molecules of isoniazid will penetrate caseous material, better than streptomycin and will reach more tubercle bacilli buried deeply in caseous lesions. One of the most striking results of isoniazid treatment is in tuberculous meningitis where the saving of lives has been increased from an average around 20 per cent of all forms of meningitis to around 60 per cent, although other factors have entered in, such as earlier diagnosis and better regulated and uninterrupted treatment.

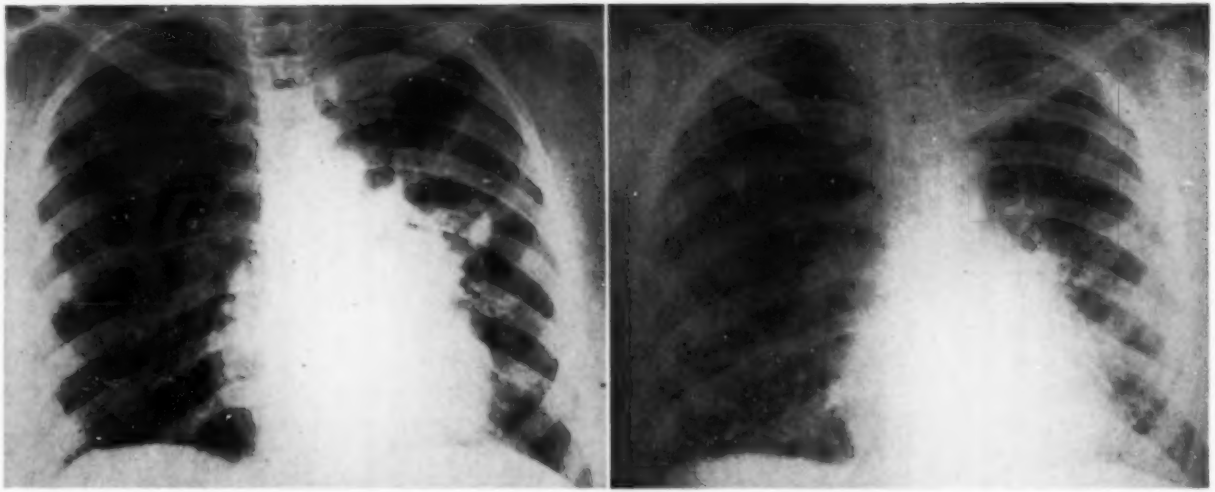

FIGURE 1 FIGURE 2

Figure 1: Copy of chest roentgenogram taken July 10, 1952 of E. K., Case No. 2840—a 30 year old colored female before treatment.—*Figure 2:* Same as Figure 1 on January 31, 1953 after five months and 20 days treatment with INAH alone. Two large annular shadows in the left lung have disappeared from view together with much clearing of other lesions. Sputum is negative.

At present it may be affirmed that there is yet no ideal chemotherapeutic agent against the tubercle bacillus. None of them are directly bacteriocidal. Isoniazid especially is only active against tubercle bacilli that are undergoing metabolic activity and are multiplying by cell division. There are undoubtedly dormant phases of tubercle bacilli that are not touched by isoniazid or even streptomycin. These are the "sleepers" that come out later on and reactivate disease after it was apparently on the way to quiescence and cure.

The most unfavorable feature of the action of isoniazid on tuberculosis is the development of resistance of bacilli against the drug. It is even more marked than that observed against streptomycin. Combining isoniazid with streptomycin does not reduce the development of resistance in bacilli against the isoniazid as much as against streptomycin which does reveal a considerable delay in resistance as a result of the presence of isoniazid. It is even more marked than the reduction in resistance produced by PAS. This feature has been demonstrated by the United States Public Health Service study.[12] In this study isoniazid was better than PAS in preventing bacillary resistance to streptomycin, but the presence of streptomycin reduced the development of resistance to isoniazid only from about 50 per cent to about 20 per cent. The conversion rate of streptomycin and isoniazid was much more than isoniazid alone and more than the combination streptomycin and PAS.

There are many unexplored phases of the action of isoniazid on tubercle bacilli and on the disease tuberculosis, but the combination of isoniazid and streptomycin seems to give the best results of any other combination used up to now. MacKaness and Smith[11] have shown that the combination of INAH and streptomycin has more than a simple additive effect of the two agents. Bacilli are inhibited in concentrations in lower dilutions of each drug in combination than in the drugs when used alone. This observation has been borne out by the United States Public Health Service study.[12] The future may unfold many other useful combinations with such drugs as PAS or with streptomycin and PAS together with INAH. Perhaps there is no greater usefulness of isoniazid than in cases with resistance to streptomycin and or PAS.

It is our pleasure to report on a limited study carried on at the Southwest Florida Tuberculosis Hospital. A brief summary of the work will be given at this time. It consists of two parts—26 cases treated with INAH alone and 10 with INAH and streptomycin.

The indications for isoniazid are little different than those for streptomycin. Without going into all the various types of tuberculosis where it produces best results, let it be said that the acute, infiltrative, and recently formed lesions respond best. Or put in another way, it is best where the drug is most readily accessible to growing tubercle bacilli. It doesn't matter whether the lesions are large or small or have an inflammatory (exudative) or fibroplastic (productive) tendency. The important feature is the accessibility of the drug to rapidly growing tubercle bacilli. Infiltrative, bron-

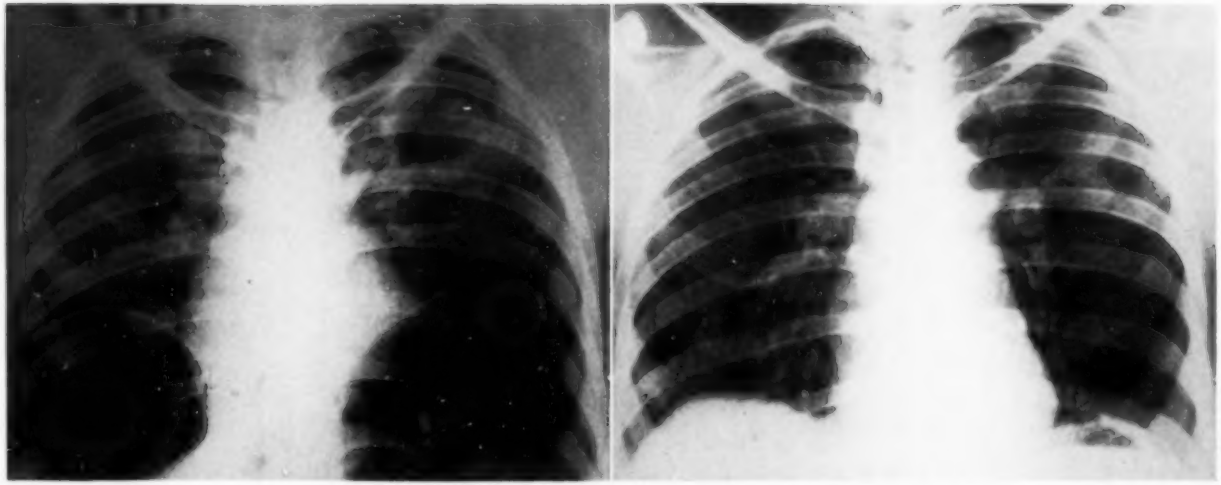

FIGURE 3 FIGURE 4

Figure 3: Copy of roentgenogram of patient F. F. on July 25, 1952. Case No. 2539 — a 34 year old colored female before treatment.—*Figure 4:* Same as Figure 3 on March 21, 1953 after seven months and 20 days of treatment with INAH alone. Note the clearing of infiltrations and the shrinking of the cavity in left midfield.

chopneumonia, pneumonic, miliary, and small nodular lesions, therefore, respond best.

On the other hand, old fibrotic types where the bacilli are sluggish in growth or are buried deeply in fibrotic tissue or in caseous masses, the effect is much less or not at all. Heavily encapsulated and partially calcified lesions show little response.

The toxicity of INAH in dosage less than 5 mgs. per kilo, is not serious except in central nervous system disease such as epilepsy, schizophrenia, etc. Outside of these conditions the most common complication, that is annoying, but not critical is an allergic reaction. There were two cases among those being reported where allergy was present, one was fleeting and soon passed off, but the other was serious, producing high fever, nausea, headache, malaise, itching, and marked erythema. Benadryl controlled the most of the unpleasant symptoms. After several attempts to resume treatment, it was found necessary to desensitize the patient by using a small initial dose and adding 1 mg. a day until 200 mgs. a day were tolerated without ill effects.

Selection of Cases:

There were 26 cases in the first group treated with INAH alone for a minimal period of three and one-half months and a maximum period of 10 months. The dose was 150 mgs. per day in patients weighing less than 100 pounds at the beginning of treatment; 200 mgs. per day in those weighing from 100 to 135 pounds; and 250 mgs. per day in those weighing from 135 to 170 pounds; 300 mgs. per day in those above 170 pounds. It is questionable whether more than 5 mgs. per kilo should be given. Barkley, Ebert and Koch-Weser[9] claim that large doses do not increase the therapeutic efficiency. Clinical laboratory and x-ray examinations were made monthly. In the laboratory examination the following tests were performed: Red blood count and hemoglobin; sedimentation rate; hematocrit; total protein; albumen; globulin; the A/G ratio; urea nitrogen; and urine examination.

There were 13 white and 13 colored patients; 11 male (eight white and three colored); and 15 female (five white and 10 colored). The stages of the disease were represented by 24 far advanced and two moderately advanced cases.

Results of Treatment:

Perhaps the most outstanding noticeable effect on the patient is the cessation of toxicity with corresponding increase in the feeling of well being, reduction of the temperature and pulse and tremendous increase in appetite and subsequent gain in body weight. Many cases began to show improvement the first week and some within a few days. Generally there was also a marked decrease in cough and expectoration. The cases having large cavities usually had a decrease in sputum in proportion to the extent of overall cavity closure. Some without cavity formation became entirely sputum free as well as bacillus free. Of 26 patients 21 (81.0 per cent)

FIGURE 5 FIGURE 6

Figure 5: Copy of chest roentgenogram on May 7, 1952 of P. F. Case No. 3005—a 43 year old colored male, after one month of treatment with SM and PAS.—*Figure 6:* Same as Figure 3 after four months treatment with SM and PAS. Note the annular shadow has enlarged but infiltrations have largely disappeared.

showed moderate to marked improvement, and all but one showed some improvement.

Weight gain was equally impressive. Of the 26 cases 12 (46.1 per cent) gained 20 pounds or more; five (19.2 per cent) gained from 10 to 20 pounds; and eight (30.6 per cent) gained one to 10 pounds. All but one gained weight.

There is nothing remarkable in the results in sex or race as they all seemed to react similarly.

Radiological changes were slower to appear than some of the clinical changes, yet after several months the changes became striking and in the same order as the clinical changes. The most dramatic change is in cavity shrinkage and closure. Sometimes the cavity will shrink to half or a third of its original size and then enlarge again which may be a result of the development of resistance in the bacilli. One case having surgery, revealed a small stellate cavity about a fifth the original size on pathological examination. The figures for marked improvement are, 11 (42.30 per cent); for moderate improvement, five (19.2 per cent); with two showing no change and three (11.5 per cent) showing deterioration and spread of the lesions. There was no race and sex difference worthy of mention. There were 16 cases (61.1 per cent) showing moderate to marked improvement.

Laboratory Changes:

The sputum was changed from positive to negative ("converted," "reverted") in 11 cases (44 per cent) out of 25. One case had a lobectomy and was treated after the operation but was never positive after the lobectomy. The other 14 cases remained positive, but the quantity of sputum was reduced in practically all.

Resistance of Bacilli:

Of the 14 cases tested for virulence, three did not have sufficient growth for testing; one was resistant to 0.2 mcgms.; four to 1 mcg.; one partially to 5 mcgms.; and five completely resistant to 5 mcg. From experience, it has been observed that partial resistance does not necessarily mean that clinical results may not still be obtained. In the 11 that were tested, however, five (45.5 per cent) were completely resistant and were beyond the point where any more treatment would give material benefit. If we add the one case partially resistant to 5 mcgs. it makes six cases (55.6 per cent) with a resistance that practically prohibits further treatment.

The Blood Cytology:

There was a consistent change in the majority of cases from an inflammatory type of blood cytology towards a normal. There was slight increase of red cells and hemoglobin, a decrease of the white blood count, and a marked lowering of the sedimentation rate.

The Blood Chemistry:

The blood chemistry was noted for the change towards normal of the albumen-globulin ratio. There were 15 of 20 cases (75 per cent) showing

an increased trend towards normal with five cases (25 per cent) a decrease in ratio. The general trend of an increase in albumen and a decrease in globulin in healing is an old and reliable index of improvement.

The blood urea nitrogen in almost all cases showed a rise in the beginning from 15 to 50 per cent, but usually levelled off or decreased after a few months of treatment and nothing of a serious nature developed in any of the cases treated.

Isoniazid with Streptomycin:

Of the 10 cases treated with streptomycin and INAH, the results were more impressive than when isoniazid was used alone. All cases were far advanced and three fourths gms. streptomycin was given intramuscularly twice a week.

The number of cases were too few to do anything more than generalize. Surely there was nothing to be said against the combination as no unusual toxicity was noted and the results were as good or better than those treated in the first series.

There was improvement in all 10 cases with nine gaining more than 10 pounds in weight; one less than 10 pounds while only one lost weight.

The blood cytology changed for the better in almost every case. The red cells and hemoglobin increased, the white cells decreased, and the sedimentation rate decreased. The blood chemistry revealed a favorable change in the protein quotient in all eight cases tested.

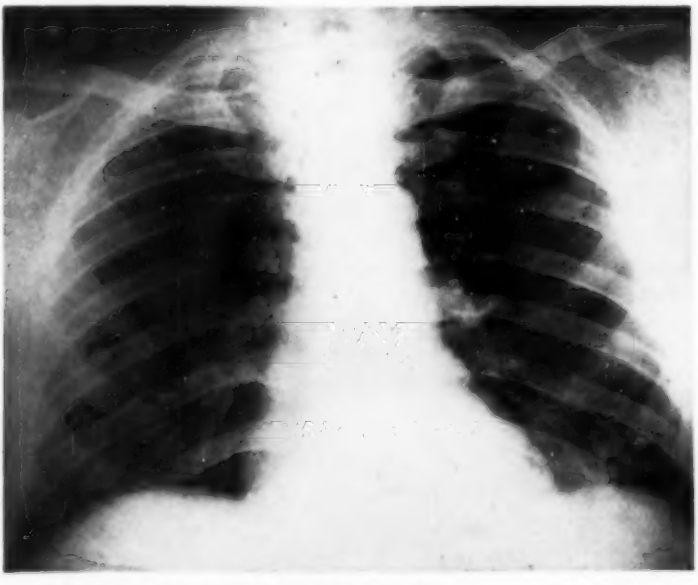

FIGURE 7: Same as Figure 3 on March 18, 1953 after seven months treatment with INAH and 11 months of SM and PAS. The annular shadow has disappeared from view but the upper wall may still be outlined.

Five cases were negative on gastric lavage after the treatment, one positive on culture and four positive on smear.

Radiologically, all 10 cases showed improvement; six marked, one moderate, and three slight.

The resistance studies were done on four of the five cases on which positive cultures were obtained. All were sensitive to 10 mcgms. streptomycin. Two were resistant to 1 mcg. INAH and two (50 per cent) to 5 mcgms. of INAH, agreement with the report of Ferebee and Long.[13] There was no striking decrease in the resistance as a result of the presence of streptomycin although the number was too small to be of significance.

Discussion:

A few observations were recorded in this study that are worthy of comment. First, is the generally favorable results in cases treated with INAH and the lack of serious toxic effects. No permanent toxicity was found, but one case had a marked urticaria that disappeared after desensitation. The results were comparable to those treated with streptomycin, but probably were not as good as streptomycin and PAS although in the small series it was difficult to determine. The addition of streptomycin seemed to enhance the results and afford a good combination—as good or better—than streptomycin and PAS.

If the INAH does protect against resistance to streptomycin according to the reports it will be a great advantage as INAH is much easier to administer than PAS. Perhaps it will be better to give all three drugs together.

There is no question but that the death rate has been lowered for tuberculosis by streptomycin, PAS and INAH, but how much, has been a true lowering of death rate or a temporary prolongation of life, is not definite. It is probable that both exist.

A most important report has been given by Klée[14] from the Wuppertal-Elberfeld Municipal Hospital, Germany, to the effect that the death rate of the hospital was around 36 per cent in 1938, in 1940 it rose to 43.3 per cent and to 46.6 per cent in 1941 during the War. In 1946, after the war was over it dropped to 39.2 per cent then plunged to 12.3 per cent by 1949 (streptomycin, PAS and tibione effect). Then it rose to 13.3 per cent in 1949 and plunged again to 0.9 per cent in 1952 after INAH had been introduced. It is difficult to see how a fall from 39.3 to 0.9 per cent in six years can be anything else but a true increase in life saving.

It has been estimated that deaths from clinical tuberculosis have decreased from near 100 per cent 75 years ago to only about 25 per cent today—and it is still decreasing! Perhaps we shall soon see the figures drop to 20, 10 per cent or to a stable figure that can be considered an "irreducible minimum" like those found in many other infectious diseases prevalent in the last century.

We are finally able to confirm what was suspected when INAH was first heralded in such glowing terms, viz: that the first flush of success was probably deceiving. It is now certain that the drug alone soon "burns out"

its usefulness. It must be used to the greatest advantage before resistance develops by saving it till the most opportune time, or by combining it with other agents to effect a mutual reduction in resistance. Undoubtedly there will be further improvements made. It is clear that the drug should not be given without careful supervision. Otherwise the "ammunition" will be wasted before the "enemy" is subdued. In fact the "ammunition" will be worse than wasted, because the premature and uncontrolled use of the drug only allows the "enemy" to develop a complete resistance after which the drug becomes useless.

These facts are presented to warn those who would go their own way in treatment and take the drug simply because it is easily self administered. It is even more important that physicians should learn how to get the maximum results with the drug. "Home Treatment" for a patient who is found to have active tuberculosis is, therefore, not at all wise unless every control measure is used that is employed in the hospital. Since few patients can be treated as in a hospital the admonition is not to take home treatment at all during the early phases of active disease!

There comes a time, however, when the patient will capitalize on the saving brought about by good management. After the acute disease has been suppressed, all symptoms have gone, the weight has increased, the x-ray film shadows are gone or disappearing and the patient is "negative" for virulent tubercle bacilli, the patient may be released weeks and even months before he otherwise would have been and treated at home by competent physicians. The time is here when the follow-up of such patients must be done in competent out-patient clinics or by the Health Department.

Still more saving of time is being made by a skillful application of surgery. When the drugs have cleared up most of the disease and cavities or masses still remain, surgery is a saving grace that has no equal in eradicating the unhealed residues just as the older surgeons would curette a carbuncle. Recovery from the surgery requires about a third the time that is required to heal the disease without it, besides surgery is more final in effecting a cure of the process.

A word of warning should also be issued to those who administer Recalcitrant Patient Laws. Before any commitment order is issued it should be made certain that the patient has bacilli in sputum that will kill guinea pigs. The new drugs are producing many bacilli that can be demonstrated on smear but they are not virulent or will otherwise not cause infection in animals, in spite of the fact that the x-ray film may show infiltrates. If it can't be proved that the secretions coming from the patient will cause infection, it seems clear that no patient can be forcibly confined irrespective of the x-ray film shadows or even the staining reactions. A test on this type of case might well cause the law to become invalid.

SUMMARY

1) An attempt has been made to place isoniazid in its proper therapeutic position and to present the theories of its action.

2) This objective has been aided by a study of the effect of INAH in the

treatment of 26 patients with pulmonary tuberculosis, as well as the treatment of 10 tuberculous patients with combined INAH and streptomycin.

3) The indications for treatment may be briefly stated as proper in all cases having acute, infiltrative components in the process. The more acute the lesions, the better the results, with a decreasing effectiveness as fibrosis exists or develops.

4) In cases still having bacilli present in the sputum isoniazid alone in 8 to 12 weeks time causes a crippling resistance to develop in the bacilli in over half the cases but with streptomycin added the resistance is reduced to less than 20 per cent.

5) According to the best information, isoniazid causes a reduction in resistance of bacilli to streptomycin, but there is still twice the resistance that develops when PAS is used.

6) The effect of INAH may be divided into two components, viz: the effect on the bacillus and the effect on the patient. The effect on the bacillus is only superficially understood at present, except that they soon cease to multiply and tend to gradually disappear from the lesions. The action is not bacteriocidal but probably the metabolism of the bacillus is suspended. Eleven of 25 cases of the first series (44 per cent) were changed from positive to negative. After two months, resistance (to five mcgms. of INAH per ml.) appears in over 50 per cent of the cultures.

7) The properly selected patient reacts rather promptly in what may prove to be a combination of non-specific stimulation and the result of the removal of toxicity of the infection. As a result, the patient promptly feels better, at times almost exhilarated. The temperature and pulse begin to approach the normal, the appetite improves, with a resulting gain in weight, and the x-ray and laboratory findings generally show a corresponding favorable change. Many times the patient feels better and desires to take exercise more than the anatomical changes of the disease warrants.

8) In the 26 cases treated with isoniazid there was a general and unmistakable improvement in all but one. In 12 there was marked improvement, in nine moderate improvement, and in four slight improvement. There was no noticeable sex and race differences.

9) The weight changes paralleled the clinical findings. There were 12 patients who gained over 20 pounds; five gained between 10 and 20 pounds and eight gained between one and 10 pounds.

10) Radiological change lagged slightly behind clinical changes. There were 11 that showed marked improvement; five moderate improvement; and five slight improvement. Two showed no change and three showed slight progression of the lesions. Moderate to marked improvement was observed in 16 cases (61.6 per cent).

11) The addition of streptomycin to the INAH treatment in 10 cases had no outstanding changes over those found for INAH. Nine (90 per cent) gained more than 10 pounds in weight and all improved as shown by clinical, x-ray film, and laboratory findings. These changes were generally similar, but more marked, than those listed for INAH alone.

12) Of four cases (40 per cent) of the combined therapy on which bacilli

could be tested all were sensitive to 10 mcgms. streptomycin, two were resistant to 1 mcgm. INAH and two (50 per cent) to 5 mcgms. The number was too small to be significant. Other studies reveal a resistance of less than 20 per cent.

13) In spite of rather dramatic effects of isoniazid treatment, patients should be hospitalized and treated by a full drug regimen during the acute stages of the disease, but many weeks and months may be saved toward the end of treatment when the patient may be treated at home under proper supervision.

14) Patients having residual infiltrates and heavy walled cavities may also have many months cut off of hospital stage by removal of the disease process by surgical excision or collapse along with, or after drug and antibiotic therapy.

RESUMEN

1) Se intenta colocar la isoniacida en su posición adecuada en la terapéutica y presentar las teorias sobre su acción.

2) Este objetivo, ha sido accesible gracias al estudio de 26 enfermos con INAH, así como el estudio de 10 enfermos tuberculosos con INAH combinada con estreptomicina.

3) Las indicaciones para el tratamiento, pueden ser brevemente consideradas como adecuadas en todos los casos con lesiones agudas e infiltrativas. Mientras más agudas son las lesiones, mejores son los resultados, decreciendo su efectividad a medida que se presenta o se desarrolla la fibrosis.

4) En los casos en que hay bacilos en los esputos, la isoniacida sola, causa una aparición de resistencia de las 8 a 12 semanas en la mitad de los casos, pero si se agrega la estreptomicina la resistencia se reduce a menos del 20 por ciento.

5) La isoniacida permite el desarrollo de la resistencia a la estreptomicina en casi la mitad de los casos en comparación con el PAS. Esta combinación por tanto, es la mejor referida hasta ahora.

6) El efecto de la INAH, puede dividirse en dos componentes: El efecto sobre el bacilo y el efecto sobre el enfermo. El efecto sobre el bacilo es sólo superficialmente comprendido hasta hoy; sólo se sabe que el bacilo cesa de multiplicarse y tiende a desaparecer gradualmente de las lesiones. La acción no es bactericida, sino probablemente se afecta el metabolismo del bacilo, suspendiéndolo. Once de 25 casos en la primera serie (44 por ciento) cambiaron de positivos a negativos. Después de dos meses, la resistencia (a 4 microgramos de INAH por ml.) aparece en el 50 por ciento de los cultivos.

7) El enfermo escogido adecuadamente reacciona pronto de manera que puede considerarse demostrativa de que existe una combinación de estímulo no específico y el resultado de la supresión de la infección. Como resultado el enfermo se siente pronto bien, a veces eufórico. La temperatura y el pulso, empiezan a aproximarse a lo normal, el apetito mejora con resultante aumento de peso y a los rayos X y al laboratorio los hallazgos

muestran un cambio favorable correlativo. Muchas veces el enfermo se siente mejor y desea hacer ejercicio más de lo que los cambios anatómicos permitirían.

8) Sólo en uno de los 26 casos, dejó de presentarse una mejoría general inconfundible. En 12, hubo marcada mejoría, en nueve moderada y en 4 ligera mejoría. No hubo diferencias apreciables en las diferentes razas y sexos.

9) Los cambios en el peso, son paralelos a los cambios clínicos. Hubo 12 enfermos que aumentaron más de 20 libras; 5 aumentaron entre 10 y 20 libras, y ocho sólo entre una y diez.

10) El cambio radiológico fué ligeramente más lento que el clínico. Hubo 11 que mostraron mejoría marcada, cinco con moderada y cinco con ligera mejoría. Dos no mostraron cambio y tres tuvieron ligero empeoramiento. En 16 casos (61 por ciento) se observó de moderada a marcada mejoría.

11) El agregar estreptomicina a la INAH en 10 casos, no produjo notables cambios sobre los encontrados con solo la INAH. Nueve (90 por ciento) subieron más de 10 libras de peso y todos mejoraron según los hallazgos clínicos, radiológicos y de laboratorio. Estos cambios, fueron similares, pero más marcados que los señalados para la INAH sola.

12) De cuatro casos (40 por ciento) entre los de tratamiento combinado, en los que el bacilo pudo ser estudiado, todos eran sensibles para 10 microgrs. de estreptomicina, dos eran resistentes a un microgr. de INAH y dos (50 por ciento) a cinco microgrs. El número fué muy pequeño para tener significación. Otros estudios revelan resistencias de menos de 20 por ciento.

13) A pesar del efecto dramático del tratamiento con la isoniacida, los enfermos deben ser hospitalizados y tratados con un régimen completo de drogas durante las etapas agudas de la enfermedad, pero muchas semanas y meses pueden ahorrarse para llevar al enfermo al fin, cuando el mismo, pueda tratarse en su domicilio bajo adecuada vigilancia.

14) Los enfermos que tienen infiltrados residuales y cavidades con paredes gruesas, pueden también ahorrarse muchos meses de estancia en el hospital para hacerse resección o colapso quirúrgico tratándose al mismo tiempo o después, con los antibióticos y estas drogas.

RESUME

1) Les auteurs font un effort pour mettre l'isoniazide à sa place exacte dans la thérapeutique et pour étudier le mécanisme de son action.

2) Cet objectif à été favorisé par une étude sur l'effet de l'isoniazide dans le traitement de 26 malades, atteints de tuberculose pulmonaire, ainsi que par le traitement de dix tuberculeux où furent associée l'isoniazide et la streptomycine.

3) Les indications du traitement peuvent être rapidement établies comme convenant à tous les cas aigus, avec processus infiltratif. Plus les lésions sont aigues, plus les résultats sont bons, avec une diminution des lésions des qu'il existe une tuberculose fibreuse on dès qu'elle se développe.

4) Dans les cas qui ont encore des bacilles dans leur expectoration, l'isoniazide administré isolément détermine en huit à douze semaines une

résistance au développement des bacilles dans plus de la moitié des cas, mais lorsque la streptomycine est associée, cette résistance se réduit à moins de 20% des cas.

5) L'isoniazide associée à la streptomycine détermine environ deux fois moins de résistance que le P.A.S. La combinaison streptomycine-isoniazide est ainsi la meilleure connue jusqu'à présent.

6) L'effet de l'isoniazide doit se diviser en deux parties: l'effet sur le bacille, l'effet sur le malade. L'action sur les bacilles est connue jusqu'à présent seulement d'une façon superficielle. On sait simplement que très vite, ils cessent de se multiplier, et qu'ils tendent à disparaitre progressivement des lésions. L'action n'est pas bactéricide, mais vraisemblablement, il y à un trouble profonddu métabolisme du bacille. Onze des vingt-cinq cas de la première série, soit 44%, virent l'expectoration se transformer de positive en négative. Après deux mois, la résistance (jusqu-à 5 gammas d'isoniazide par cc.) apparut dans plus de 50% des cultures.

7) Les malades bien choisis eurent des réactions assez rapides qui semblent indiquer qu'il y à combinaison d'une stimulation non spécifique et de la disparition de la toxicité de l'infection. Le malade très rapidement se sent mieux, parfois même tout à fait euphorique, la température et le pouls commencent à tendre à la normale, l'appétit s'améliore avec une augmentation de poids, et les constatations radiologiques et biologiques en général montrent parallèlement des modifications favorables. Souvent le malade se sent mieux, et désire reprendre une activité plus importante que ne le permettent les modifications anatomiques des lésions.

8) Dans 26 cas qui ont été traités avec l'isoniazide, il y à d'une façon générale amélioration incontestable dans tous les cas sauf un. Dans douze cas, il y eut une amélioration nette, dans neuf cas modérée, et dans quatre cas légère. Il n'y eut aucune différence notable selon le sexe ou la race.

9) Le poids se modifia parallèlement aux constations cliniques. Douze malades augmentèrent de plus de 20 livres, cinq augmentèrent de 10 à 20 livres, et huit entre une et dix livres.

10) Les modifications radiologiques se montrent assez inférieures aux modifications cliniques. Onze malades eurent une amélioration nette, cinq une amélioration modérée, et cinq autres une amélioration légère. Chez deux malades, il n'y eut aucune modification, et trois autres montrèrent une légère aggravation des lésions. Chez 16 malades (61%) on nota une amélioration oscillant de l'amélioration modérée à l'amélioration très nette.

11) L'association de streptomycine chez dix malades ne donna pas une modification considérable des constations faites avec l'isoniazide isolé. Neuf d'entre eux (90%) augmentèrent de plus de 10 livres, et tous s'améliorèrent cliniquement, radiologiquement, et biologiquement. Cette évolution généralement fut similaire et non supérieure à celle qui fut obtenue par l'isoniazide isolément.

12) Parmi ces cas où la thérapeutique associée fut instituée, quatre (40%) pour lesquels fut mesurée la résistance des bacilles, tous se montrèrent sensibles à 10 gammas de streptomycine, deux furent résistants è un gamma d'isoniazide et deux (50%) à cinq gammas d'isoniazide. Le nomtre

est trop petit pour avoir une valeur quelconque. D'autres études montrent une résistance de moins de 20%.

13) Malgré l'effet relativement sensationnel du traitement par l'isoniazide, les malades devraient être hospitalisés et traités par le régime complet pendant la phase aigue de la maladie mais le malade peut ensuite être traité pendant de nombreuses semaines et de nombreux mois vers la fin de ce traitement, à domicile à condition d'être bien contrôlé.

14) Les malades ayant des infiltrats résiduels et des cavités à parois épaisses, peuvent également avoir leur temps d'hospitalisation considérablement réduit en supprimant la lésion par exérèse chirurgicale, par collapsus, avec l'aide de la chimiothérapie et du traitement antibiotique.

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Iproniazid in Pulmonary Tuberculosis*

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The initial studies of the hydrazides in tuberculosis concerned chiefly the isopropyl derivative of isonicotinic acid or iproniazid; the parent compound, isoniazid, received secondary consideration. In their report, Selikoff and Robitzek[1] detailed their experience with 92 patients, 82 treated with iproniazid and 10 with isoniazid. The early availability of the latter and its comparatively low toxicity were instrumental in the immediate acceptance of this drug as the preferred antibacterial agent although, on the basis of the original observations by the authors mentioned, iproniazid seemed more potent.

In an attempt to assess the relative merits of the two drugs, a study of iproniazid†† was begun in July, 1952 and concluded in June, 1953, utilizing a small group of patients clinically comparable to a larger number concurrently under treatment with isoniazid.[2] As a result of information which was rapidly accumulating on the toxicity of iproniazid, and through personal experience, the patients were under particularly careful supervision and at the first sign of untoward effects the medication was discontinued. This largely explains why the results of the study with iproniazid were not as definitive as those obtained with isoniazid, also the relatively mild range of toxic reactions encountered.

Composition of Material

Fifty-two patients with pulmonary tuberculosis were treated with iproniazid. The results of three are not included because of the multiplicity of agents used. The age, sex and racial composition of the 49 patients analyzed are shown in Table I. With rare exceptions all had advanced bilateral disease. Approximately 70 per cent were Negroes or Puerto Ricans who notoriously have low resistance to tuberculosis. Only one patient had predominantly chronic pulmonary tuberculosis, the remainder had either initially acute (36 patients) or "acute-on-chronic" disease (12 patients). Twenty-seven, or more than half, were newly admitted who had had no treatment for their tuberculosis previously. Two had had collapse therapy only. Ten had had antibacterial treatment only and the remaining 10 antibacterial plus collapse measures. Of the 20 who had received antibacterial treatment, 13 had had streptomycin (dihydrostreptomycin) plus para-aminosalicylic acid (PAS) and seven, isoniazid.

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††Iproniazid (Marsilid) was supplied through the courtesy of Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Dosage Schedules

The maximum amount of iproniazid given daily was 200 mg., in three divided doses, corresponding to less than 4 mg. per kg. of body weight. Eight received 100 to 125 mg. daily, either because the weight of the patient was less than 100 pounds or, in some instances, as an added precaution against toxic effects. During the period of iproniazid medication no other antibacterial treatment was given, with one exception. The particular patient had received a course of dihydrostreptomycin plus isoniazid with a satisfactory symptomatic response but without effect roentgenologically. After a three months' trial with iproniazid alone, dihydrostreptomycin was added without apparent benefit from either. The duration of iproniazid treatment for the entire group ranged from 11 days to five and one-half months; only five received the drug longer than four months. Prior to the institution of iproniazid treatment, the patients had new blood counts, liver and kidney function tests.

Results

Subjective: The symptomatic effects of iproniazid were excellent considering the short period of medication in most cases. Of the entire group only two failed to show a favorable response in one way or another. Seventeen who had had temperatures persistently over 100 degrees F. (several, 103 to 104 degrees F.) showed a return to normal levels within four to 14 days, the majority in the shorter time interval. Weight gain varied from four to 46 pounds, depending on the length of treatment; three failed to show gain in weight. The amount of expectoration decreased rapidly. Thirty-two had had moderate to copious amounts of sputum. After institution of iproniazid treatment, nine showed a mild degree, 16 a moderate and seven a marked degree of reduction in the daily amount of sputum. The effects of the drug often became evident within a few days of the beginning of treatment.

Objective: In assessing the results of treatment of pulmonary tuberculosis, the greatest weight is rightly placed on bacteriological findings and

TABLE I

DISTRIBUTION OF PATIENTS ACCORDING TO AGE, SEX AND RACE*

Age Group	MALE			FEMALE			
	W.	N.	P.R.	W.	N.	P.R.	Total
Under 20		1		2	2	1	6
21 to 30		4		3	5	3	15
31 to 40	1	5	2	1	5	1	15
41 to 50	6	1		1	2		10
Over 50	1	2					3
TOTALS	8	13	2	7	14	5	49

* W, White; N, Negro; P.R., Puerto Rican.

on changes in serial chest x-ray films. Because of the relatively short duration of treatment in the majority of the patients, the immediate results of the bacteriologic examinations of the sputum or the gastric contents for acid fast bacilli hardly enters the discussion. The mere reduction in the amount of bacilliferous sputum undoubtedly helped prevent further spread of the disease thereby contributing to the healing process. The x-ray film findings were scored by the same yardstick applied to the group of isoniazid-treated patients. The changes in each lung were rated individually as follows: a satisfactory result in one lung was scored as 1+ or 2+ depending on the degree of improvement. No significant change was indicated by 0 and worse by W. By combining the score for each lung it was possible to arrive at a final rating of 0, 1+, 2+, 3+, 4+ or W, scores of 3+ or 4+ representing striking degrees of roentgenologic clearing.

According to this method of x-ray shadow scoring, applied in 47 patients, 18 showed 1+; 13, 2+; and two, 3+ improvement roentgenologically. Fourteen had a score of 0. The one with predominantly chronic disease who had iproniazid for 11 days scored 0. A comparison of the scores of 27 patients who had not received any form of antibacterial medication previously and 20 who had had such treatment revealed a slight advantage for the former. Of the 20 who had been treated with antimicrobial agents previously, seven had received isoniazid for at least four months. Of these, two scored 1+ and five, 0. Five of these patients received iproniazid for three months or longer. Because of the wide variations in treatment periods of individual patients and the comparatively short duration of treatment for the group as a whole, the results, although substantial, were inconclusive as a gauge of the relative effectiveness of iproniazid and isoniazid.

In 33 who showed variable degrees of roentgenologic clearing, the length of treatment ranged from two and one-half to 17 weeks, the majority eight to 11 weeks. In 15 showing no roentgenologic improvement, eight had treatment up to four weeks and seven from one and one-half to 16 weeks. Several of the latter received iproniazid primarily for its symptomatic effect. Thirty-seven showed some measure of correlation of the clinical and roentgenological findings although not necessarily to corresponding degrees, the clinical improvement at least equalling and usually surpassing the x-ray film scores. Ten of the 14 with an x-ray film score of 0 showed a satisfactory clinical response. In no instance did the x-ray film score exceed the degree of clinical improvement.

Toxic and Side Effects

Twenty-five, or approximately half of the patients treated with iproniazid, developed toxic symptoms which, in our opinion, made it advisable to discontinue the medication. Sixteen of the 25 showed toxic effects after two and one-half to five weeks of treatment, in most instances at the end of the third week. Seven developed toxic symptoms in from nine to 11 weeks. In an additional two the appearance of increasing anemia necessitated stoppage of the drug. The symptoms which prompted discontinuation of iproniazid are listed in Table II. They ranged from dizziness,

sleepiness and headache to frank psychosis. No instances were encountered of, so-called, "withdrawal" symptoms,[3,4] observed in patients under intensive iproniazid medication because few received the drug for any considerable length of time.

The potential danger of the use of anesthetics in patients under iproniazid medication, noted by others, was forcefully illustrated in three cases. Two patients receiving iproniazid were prepared with local anesthesia for bronchoscopic examinations. Both developed reactions in the form of extreme nervousness, spasms and convulsions. In one the seizure occurred at the completion of the anesthesia precluding the bronchoscopy; in the other, the seizure occurred after the bronchoscopy. The patients improved under sedation. The third experience was particularly instructive. The patient had been bronchoscoped once previously without untoward effects. A second bronchoscopy was done while the patient was receiving iproniazid and, at this time, a severe reaction occurred. After iproniazid had been discontinued for some time bronchoscopy was repeated without complications.

In 24 patients iproniazid was discontinued for non-toxic reasons. Six left the hospital after periods of treatment ranging from three to 12 weeks. Two others showed no results and an additional two showed early improvement which soon reached a plateau. In one iproniazid was discontinued after two and one-half weeks of treatment because of complicating pregnancy. In five the purpose for instituting iproniazid treatment was accomplished. These patients had hyperacute disease and responded well to the drug but because they were in need of long-term treatment it seemed preferable to place them on other antibacterial medication. There were eight who were surgical prospects. One showed mild toxic effects after three weeks of iproniazid but might have continued treatment longer; the others had been receiving medication for periods ranging from seven

TABLE II

TOXIC SYMPTOMS ENCOUNTERED IN 25 PATIENTS*

Dizziness	17
Sleepiness	2
Headache	1
Psychosis	1
Muscular twitchings	2
Blurring of vision	1
Fullness or ringing of ears	2
Deafness (temporary)	2
Numbness of tongue	1
Nausea	1
Constipation	3
Anemia	2
Urinary frequency	1
Liver damage	2
Weakness in the knees	1

* Some patients presented more than one symptom accounting for the discrepancy between number of patients and number of toxic symptoms.

to 14 weeks. All were placed on interrupted dihydrostreptomycin plus para-aminosalicylic acid. As a result of our study with isoniazid, we have come to the conclusion that dihydrostreptomycin plus PAS is the best combination of drugs for long sustained antibacterial effects and that the hydrazides, after the acute phase of the disease is controlled, are best held in reserve for special contingencies including surgical treatment.

Discussion

A reliable comparison of the relative effectiveness of iproniazid and isoniazid in the treatment of pulmonary tuberculosis is not possible on the basis of the present study. Only five patients received iproniazid for four months or longer (the longest five and one-half months) whereas this was the minimum test period of the isoniazid-treated group. But even on the basis of the short periods of observation, there seemed little doubt that the symptomatic effects of iproniazid were more pronounced and become evident sooner than with isoniazid. The fever declined more precipitously, the amount of expectoration decreased more rapidly and the weights reached greater magnitude in iproniazid-treated patients. Roentgenologically, improvement also appeared to register sooner in the iproniazid-treated patients. In general, iproniazid does what isoniazid does but more rapidly, especially in the way of abating acute symptoms.

There is no doubt of the greater toxicity of iproniazid as compared to isoniazid. Here we have a picture of contrasts rather than one of comparisons. Early in our isoniazid study it became apparent that toxicity was a relatively minor consideration. As the work proceded, there was less and less need for repeated blood counts, liver and kidney function tests. The patients required about the same degree of supervision as those treated with dihydrostreptomycin and para-aminosalicylic acid. With iproniazid, however, the reverse was true. Dizziness appeared early, occasionally muscle twitchings, blurring of vision, headache and other distressing symptoms, often in combination. Fortunately, the one instance of psychosis occurred early in our experience. The occurrence was so dramatic and without warning that special precautions were taken subsequently with patients who were put on the drug. Some were placed on a dosage of 100 to 125 mg. of iproniazid but the low dosage failed to show results and the dose was increased to 200 mg. daily. One developed acute, toxic symptoms while receiving only 100 mg. of the drug daily.

It is well to draw attention to seven patients who had received isoniazid previously for at least four months and who, because the improvement was slight or had levelled off, were placed on iproniazid with the hope of further gains. Although little was accomplished in the way of roentgenologic changes and slight symptomatic improvement, only one developed dizziness after one month of treatment. Another of this group received iproniazid for three months, three others for four months and one, as long as five and one-half months without toxic effects. This experience, although limited, would seem to bear out the observations of Buck and Schnitzer[5] to the effect that bacillary resistance to isoniazid also causes

increased resistance to isopropyl isoniazid. The toxic potentials of iproniazid may have also been dissipated by previous use of isoniazid but this is speculative.

SUMMARY

Forty-nine patients with advanced pulmonary tuberculosis were treated with iproniazid, the isopropyl derivative of isoniazid. The symptomatic effects of the drug, as judged by the resulting reduction of fever, decrease of sputum and increase of body weight, were more striking and became evident earlier than in a comparable group of patients treated with isoniazid alone. Regressive changes in the tuberculous process were noted in serial chest x-ray films even in the short time the majority of the patients could be kept on the drug. But the degree of symptomatic improvement almost invariably exceeded the degree of roentgenologic clearance. The development of toxic symptoms caused premature discontinuation of iproniazid in approximately half of the patients.

In the light of these observations, iproniazid alone is not recommended in the routine treatment of tuberculosis. Additional studies are in order to explore the possibility of combining iproniazid with dihydrostreptomycin and/or para-aminosalicylic acid for two or three weeks in patients with hyperacute disease as a preliminary to the placement of such individuals on prolonged medication with less toxic antimicrobial agents.

RESUMEN

Se trataron cuarenta y nueve enfermos de tuberculosis pulmonar avanzada con iproniacida, el derivado isopropílico de la isoniacida. Los efectos sintomáticos de la droga a juzgar por la disminución de la fiebre, y del esputo y aumento de peso, fueron más sorprendentes y se evidenciaron más pronto que en otro grupo de enfermos tratados con isoniacida sola.

Se notaron cambios regresivos del proceso tuberculoso en las series de radiografías en la mayoría de los enfermos aún en el corto plazo que se pudieron tratar con la droga. Pero el grado de la mejoría sintomática casi invariablemente excedió al de la limpieza radiológica. La aparición de síntomas de toxicidad motivó la suspensión de la iproniacida aproximadamente en la mitad de los enfermos. En vista de estas observaciones la iproniacida sola no es de recomendarse en el tratamiento de rutina de la tuberculosis. Se hacen estudios para determinar la posibilidad de combinar la iproniacida con dihidroestreptomicina y/o PAS por dos o tres semanas en enfermos con la afección aguda en extremo, como un preliminar al uso de otros agentes antimicrobianos menos tóxicos.

RESUME

49 malades atteints de tuberculose pulmonaire avancée furent traités par l'iproniazide, dérivé isopropyl de l'isoniazide. L'action de ce produit sur les symptômes, à en juger par l'abaissement de la fièvre, la diminution de l'expectoration et l'augmentation de poids, furent plus frappants et plus

précocément appréciables que dans un groupe comparable de malades traités par l'isoniazide seul.

Les auteurs notèrent une régression des altérations tuberculeuses sur les radiographies faites en série malgré la brièveté de la période pendant laquelle les malades furent soumis au traitement. Mais l'amélioration des symptômes dépassa presque invariablement l'amélioration des signes radiologiques.

L'apparition de signes d'intoxication nécessita la cessation prématurée de l'iproniazide dans environ la moitié des cas. A la lumière de ces observations, les auteurs ne recommandent pas l'iproniazide comme traitement de routine de la tuberculose. Des études complémentaires sont mises en oeuvre de façon à étudier la possibilité d'associer l'iproniazide à la dihydrostreptomycine et/ou au P.A.S. pendant deux ou trois semaines chez les malades atteints d'affection aiguë, avant la mise à un traitement prolongé par des agents antimicrobiens moins toxiques.

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Electrocardiographic Changes Following Pneumoperitoneum*

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In spite of the wide spread use of pneumoperitoneum as an efficient tool in the treatment of chest diseases, there is still basic disagreement in regard to its influence on the electrocardiogram. It is our feeling that a better knowledge of the electrocardiographic changes following this procedure is desirable.

It is the purpose of this study to describe such changes as we observed in a series of 25 patients and to attempt to correlate them with known electrophysiological principles.

Material and Methods:

Twenty-five subjects were selected for pneumoperitoneum therapy. Most of them suffered from moderately advanced or definitely advanced tuberculosis. None had previous collapse procedures such as pneumothorax or phrenemphraxis.

The age ranged between 16 and 46 years, the average being 25. There were 12 females and 13 males. The patients were free from organic heart diseases.

The majority were of asthenic build. Twelve lead electrocardiograms were taken before and after the procedure. The latter were recorded as a rule after the third or fourth inflation, first in recumbency, then in sitting position. The amplitude variations of the ventricular complexes in these two positions were considered unimportant for practical purposes. Accordingly, any significant change should be ascribed to the effects of pneumoperitoneum.[1,2]

For the electrocardiographic interpretation the following items were taken into consideration:

1) In the standard leads:
   a) The electrical axis of QRS.
   b) The pattern in LIII.
   c) Changes of QRS suggestive of rotation about the longitudinal and transversal axis, according to Wilson's criteria.[3]
2) In the unipolar limb leads:
   a) The "electrical" position, determined according to Wilson's criteria.[4]
   b) The pattern in aVF and aVL.

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3) In the precordial leads:
   a) The changes suggestive of a rotation about the longitudinal axis. (Wilson).
   b) The T waves.

RESULTS

A) *Electrical Axis of QRS:*

1) *In recumbency:* In all the cases, without any exception, an AQRS shift towards the left was observed. Compared to its width in the record before the procedure, the range of narrowing of the angle was from 9 to 58 degrees. In most cases there was a 20 to 30 degree shift to the left. The average model axis of QRS, computed from the 25 ECG, shifted from plus 56.8 degrees to plus 31.8 degrees.

2) *In sitting position:* The shift to the left increased, so that in 11 cases it was between 0 and minus 15 degrees. It is clearly understood that the QRS changes corresponded to an increase in height of R in lead 1 and to a more or less marked negativity in LIII. This was very often demonstrated by a deep Q_3 wave.

B) *LIII and the Deep Q_3 Wave:*

1) *In recumbency:* Before the procedure no deep Q_3 wave was observed, with the exception of two cases, which showed a 2 and 3 mm. Q_3 respectively. After inducing pneumoperitoneum, a Q_3 deflection appeared in 21 cases (84 per cent). In 15 cases this wave was larger than one half of the R wave in the same lead. Sometimes the Q_3 wave was as large or even larger than the positive deflection in this lead (Figure 1). No attempt to correlate this finding with the amplitude of the R_1 deflection was made, as it was clearly understood that these were not pathological Q waves. It was obvious, however, that the Q_3 wave surpassed a few times the "pathological" amplitude, as stated by current criteria (Myers,[4] Goldberger,[5] Ungerleider,[6] Lyle[7]).

2) *In sitting position:* These findings were more conspicuous in the sitting position. The Q_3 wave grew deeper in all the 21 cases observed in recumbency, with the exception of a single case (Figure 2); in this patient, a dominant negativity of the rSr' pattern was observed. Deep Q waves ranging from 8 to 13 mm. were recorded in the sitting position. The variation of amplitude according to respiration accounted for their positional character.

The QS complex observed in three cases was changed to a Qr complex since it took only a slight respiratory change to convert one into the other. The Q_3 duration was never longer than .04 of a second.

In four cases there was no Q_3 wave. There was, however, a dominant negativity (rS pattern) which increased in the sitting position (Figure 3). It should be emphasized that in these four cases a counterclockwise rotation of QRS about the longitudinal axis was observed. In all the other 21 cases a more or less marked clockwise rotation was found.

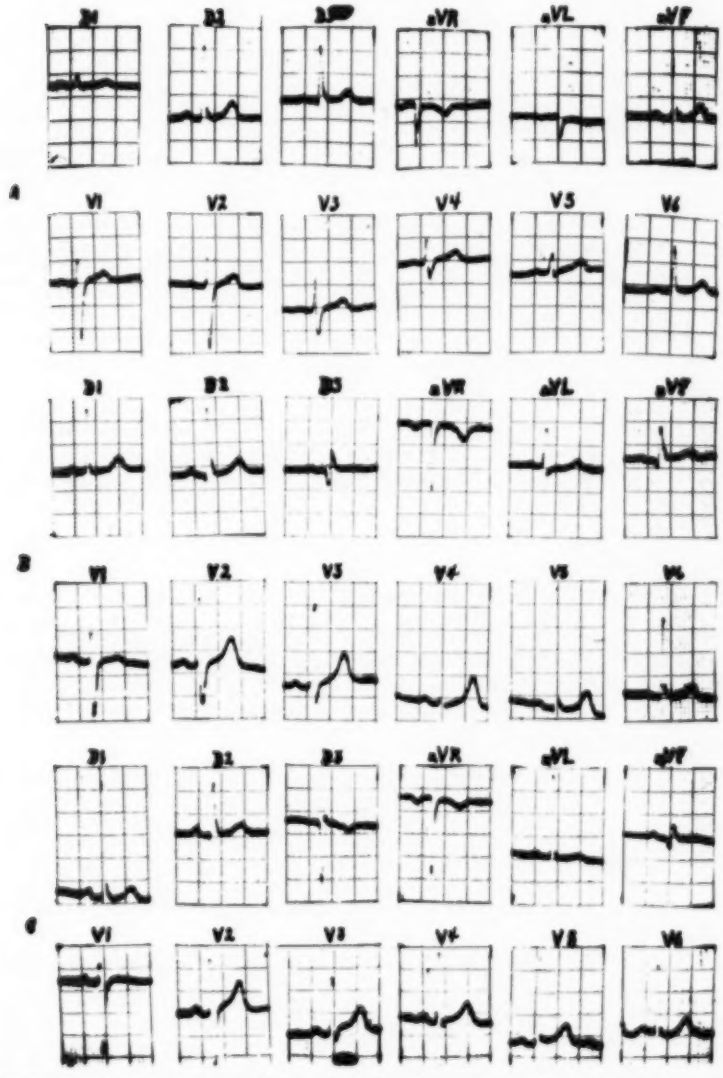

FIGURE 1: (A) Control (before pneumoperitoneum), (B) (after pneumoperitoneum), in recumbency, (C) (after pneumoperitoneum), in sitting position.

D.St.A.: A 22 year old asthenic man. Note in (B) and (C) (as in Figure 2, 4 and 5) the axis shift towards the left, the changes in electrical position, the Q_3 and QaVF waves more marked in sitting position, finally, the slight counterclockwise rotation (shift of the transitional zone).

C) *T Wave in LIII:*

The QRS left axis shift and the Q_3 wave were followed, as a rule, by T wave inversion in LIII, which was observed in 16 cases. In three cases diphasic or flat T waves were found. In sitting position the T wave inversion became more marked in 13 cases.

D) *Unipolar Limb Leads:*

aVR lead: In this lead only a few minor changes were observed. On the other hand, significant changes appeared in the aVF and aVL leads.

aVF lead: In recumbency: A Q wave in aVF ranging in size from 1 to 3 mm. was found in 10 tracings. In eight more cases in which a small Q wave was observed before the procedure, it became more pronounced afterwards. It is felt that, despite the lack of amplitude, as compared with the Q_3 wave, these QaVF waves are of some significance, as there was a trend towards the horizontal position and the R/Q ratio was diminishing.

aVF lead: In sitting position: A deepening of the Q wave was observed in six cases (2 to 3.5 mm.). On a single record a 5 mm. QaVF was found (Figure 4). As the trend towards the horizontal electrical position became more marked, such Q waves may erroneously be interpreted as "pathological," especially when no S_1 wave is observed. In two cases the Q/R ratio was greater than one.

aVL lead: In recumbency: This lead demonstrated further the shift from the vertical or semi-vertical position towards an intermediate or semi-horizontal position. This was suggested by the recording of ventricular complexes of the R, Rs or rs pattern, in 17 cases. In an attempt to correlate the finding, it was found that the initial upward deflection in aVL, corresponded to a Q wave in lead III.

aVL lead: In sitting position: This initial positivity remained constant despite the R wave increase (cf. electrical position).

In the four cases in which no Q_3 wave had been observed, the ventricular complexes in aVL were of the qR pattern.

TABLE I

POSITION	BEFORE PNP No. of Cases	AFTER PNP No. of Cases	
		Recumbency	Sitting Position
Vertical	12	3	0
Semi-vertical	7	7	3
Intermediate	2	6	3
Semi-horizontal	1	3	9
Horizontal	0	2	7
Undetermined	3	4	3

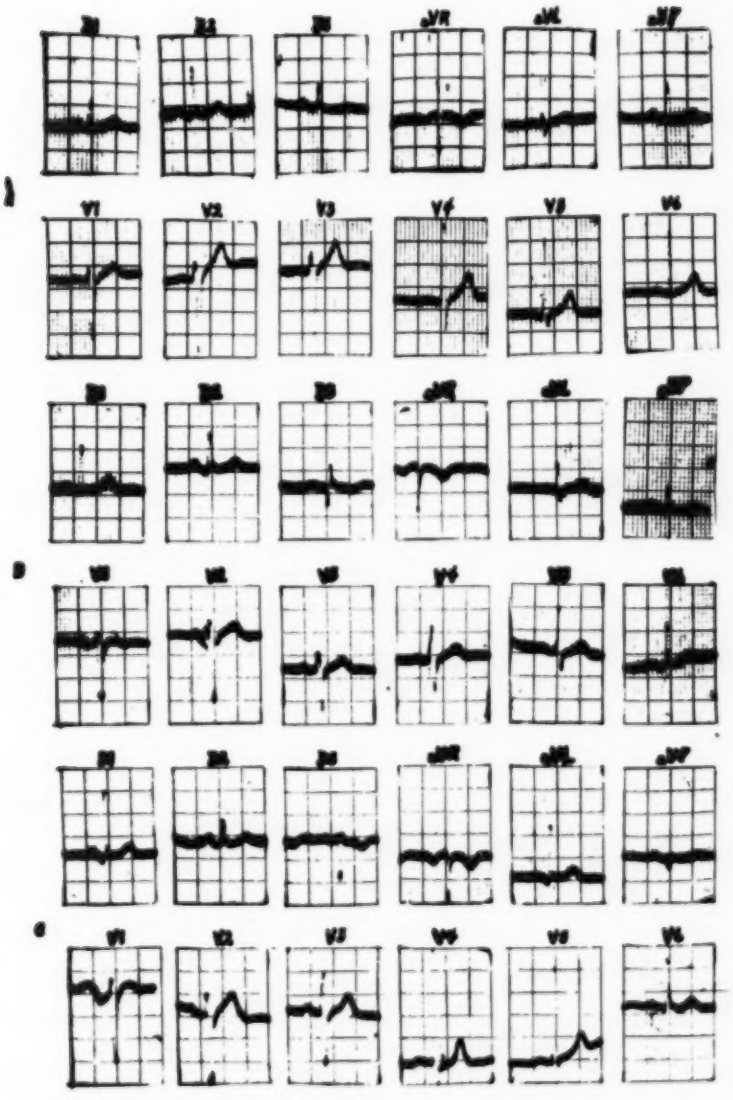

FIGURE 2: (A) control, (B) in recumbency, (C) in sitting position.

J.S.: A 39 year old asthenic man. Note the deep Q_3 wave in (B). In (C) there is a rSr' complex in LIII. Note also the appearance of a slight QaVL wave; this may account for the absence of Q_3 in (C).

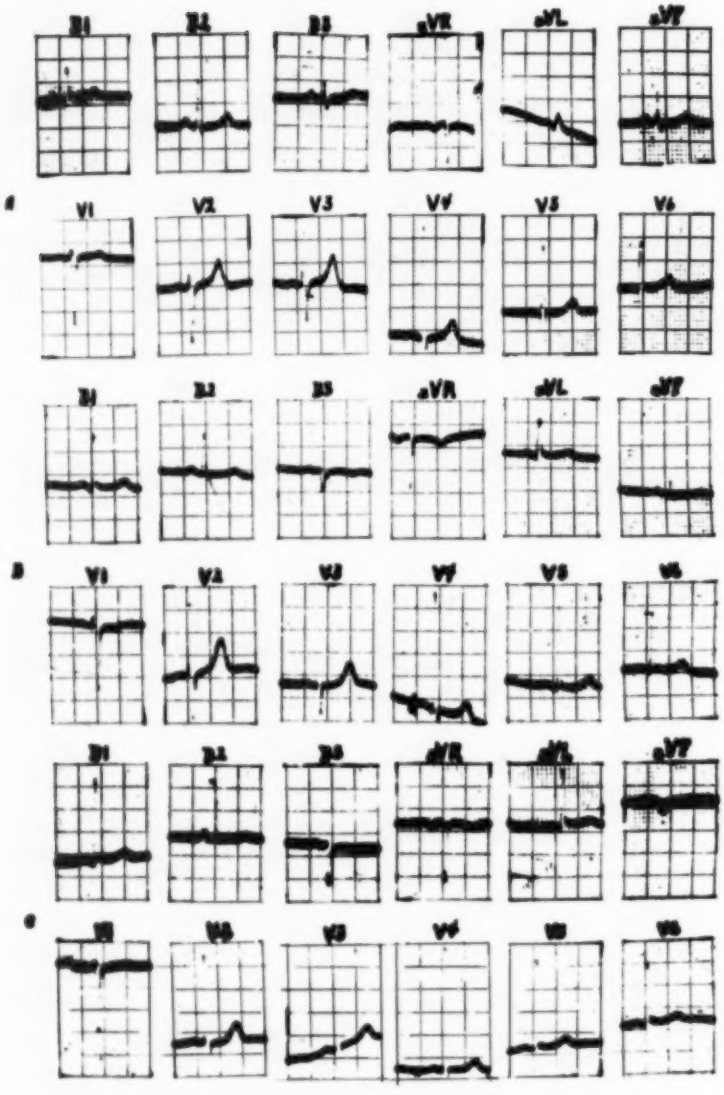

FIGURE 3: (A) control, (B) in recumbency, (C) in sitting position.

G.L.: A 44 year old asthenic man. Note in (A) the initial counterclockwise rotation (Q_1S_3). In (B) and (C) note the marked left axis shift and the counterclockwise rotation recorded also in the precordial leads. There are no Q_3 and QaVF waves.

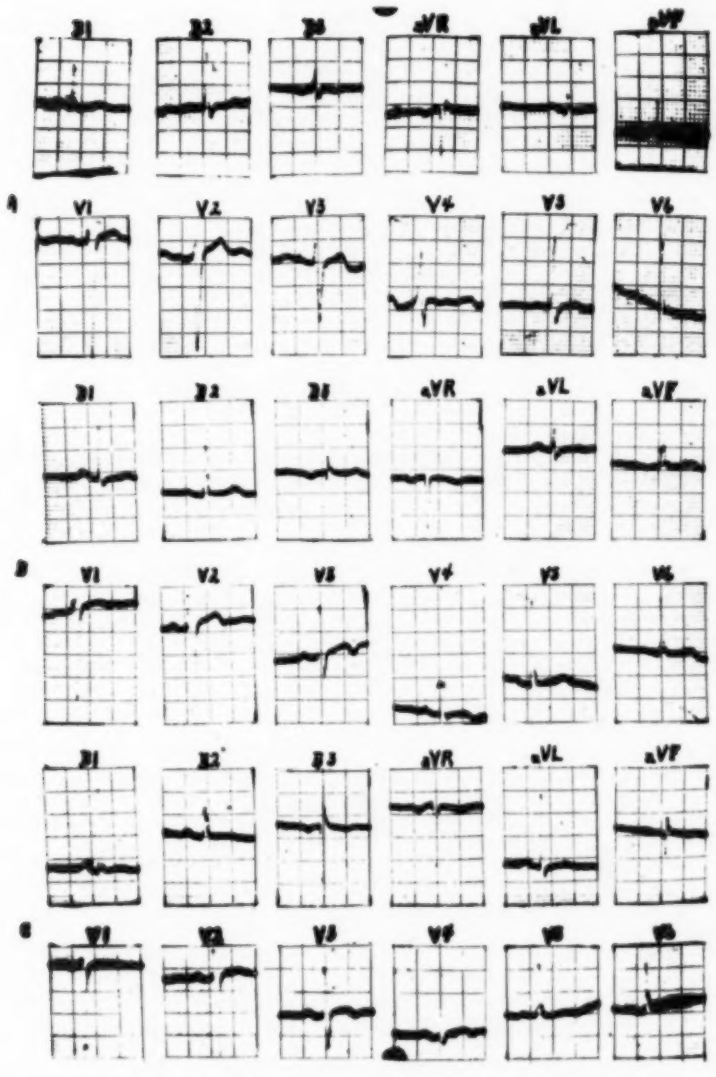

FIGURE 4: (A) control, (B) in recumbency, (C) in sitting position.

R.T.: A 21 year old asthenic man. Note besides the usual findings (cf. Figure 1) the marked Q_3 and QaVF waves in sitting position. In (B) there are inverted T waves in V_3 and V_4. In (C) the inversion reaches V_5.

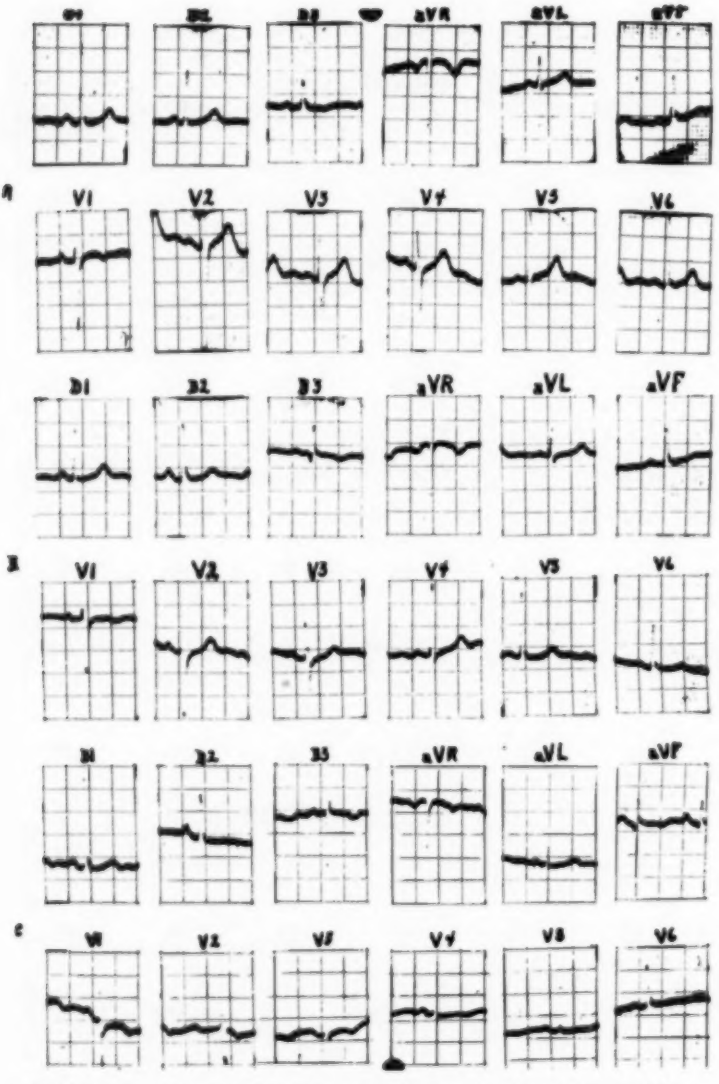

FIGURE 5: (A) control, (B) in recumbency, (C) in sitting position.

J.S.: A 31 year old asthenic woman. Note besides the usual findings the presence in (C) of inverted precordial T waves from V_1 to V_4, and flattened T waves in V_5 and V_6.

E) *"Electrical" Position:*

The changes observed in the electrical positions are tabulated in Table I.

F) *Precordial Leads:*

The transitional zone of QRS in precordial leads was shifted somewhat to the right in 15 cases after pneumoperitoneum had been induced. There was no further change in the sitting position.

Precordial T waves:

Marked changes in the precordial T waves were observed in two cases. In the first (Figure 4) there were diphasic T waves in V_2 and inverted T waves in V_3 and V_4. This inversion reached the V_5 lead in sitting position.

In the second case (Figure 5) a flattening of the precordial T waves was observed after the procedure. Furthermore, in sitting position the T waves were inverted from V_1 to V_4, and flattened in V_5 and V_6.

G) *Rotation About the Transversal Axis:*

It is well known that the heart may displace the apex forward and its basis backwards, and vice-versa. Although statistical valuable correlations between the electrocardiographic findings and the x-ray findings[9] are not available as yet, it appeared important to look for such changes, at least tentatively.

After the procedure, Q_1, Q_2, and Q_3 waves were found in seven cases. This may imply forward rotation about the transverse QRS at least from an electrophysiological point of view.

Comments

Some of the changes pointed out above were mentioned in the past, chiefly those regarding the standard leads, i.e. the left axis shift and the Q_3 wave. Such were the findings in some of the cases studied by Elwood, Piltz and Potter[10] and Benat and Berg.[11] It is surprising, however, that more recent studies by Evans and Black,[13] and Polack,[12] do not fully agree with the previous findings.

In 1950, Evans and Black reported on the presence of large Q waves in esophageal leads at the ventricular level following pneumoperitoneum. They found, however, a QaVF and QIII wave in only one of 10 cases. Furthermore, only occasionally did they notice an axis shift. Accordingly, these authors stated that the changes were of little importance. Except in three cases, these authors had no records before the procedure.

The same criticism may be used against Polack's paper (containing also an excellent survey of the problem). This author stated that there are no significant changes in recumbency; on the other hand, in sitting position she found a left axis shift in nine cases out of 16 studied, as well as a deep Q wave in four cases.

In order of frequency the changes observed in our study were as follows: A left axis shift and a trend towards the horizontal electrical position, an

appearance of a more or less deep Q_3 wave, an initial positivity in aVL, an initial downward deflection in aVF, finally a trend towards a counterclockwise rotation. The Q wave in LIII is often followed by an inverted T wave. All these changes, except the tendency to counterclockwise rotation are more marked in the sitting position.

The Q_3 wave may be considered as the most striking change. With regard to the electrophysiological mechanism involved in its appearance, the following can be stated:

1) A deep QaVF wave is generally induced by a posterior myocardial infarct. Less often, it may be seen in normal subjects when the auricular potential on the surface in vicinity of the atrio-ventricular sulcus is transmitted to the leg. Such a mechanism was suggested by Gomez in an experimental work carried out on dogs[14] and proposed by Evans, et al.,[15] and Rubin, et al.[16]

2) The Q_3 wave due to an initial positive potential in aVL occurs in some vertical or semi-horizontal hearts which are rotated clockwise about the longitudinal axis. In these cases only a part of the surface of the left ventricle is viewed by the left arm, so that the left arm leads will show no negative initial wave. Such records were observed in pregnant women.[16] In fact, the elevation of the diaphragm induces a trend to an electrical horizontal position, as demonstrated by large R waves. As a rule, despite the horizontal position, there is no QaVL deflection. This is due to the fact that under such circumstances, a heart initially vertical or semi-vertical, when subjected to significant rotation about the antero-posterior axis, is exposed only to a minimal rotation about the longitudinal axis. This does not seriously counteract the genuine clockwise rotation. The same mechanism may be present in pregnant women, in subjects with ascites, and in excessive obesity.

3) Both mechanisms herein analyzed may work separately or combined.

In the four cases without Q_3 wave, the ventricular complexes in aVL were of the qR or qRs pattern and an obvious counterclockwise rotation was noticed on the record before the procedure (Q_1 S_3 pattern).

In 10 cases QaVF waves were found after the procedure. This may account for some deep Q waves in lead III, involving the combined mechanism. Such deep QaVF waves were recorded by Rubin and Most[16] who observed that these waves were increased in expiration. A combined study with the oesophageal leads at the ventricular level, as carried out by Evans, et al. and Rubin and Most, accounts for the hypothesis that such QaVF waves may represent the transmission to the left leg of the potential of the basal-posterior surface of the heart at the level of the sulcus atrioventricularis. Such an atypical transmission is likely to be due to the forward rotation of the heart about the transverse axis. This rotation induces an elevation of the anterior surface of the heart and a corresponding descent of the posterior surface. Thus it may be assumed that the auricular zone at the level of the atrio-ventricularis sulcus descends to a level usually ventricular, and faces the diaphragm.

SUMMARY

An analysis of the electrocardiographic changes induced by pneumoperitoneum in 25 patients, studied in recumbent and sitting position, demonstrates that the changes, although significant, are exclusively positional.

In their order of frequency the changes observed were as follows: (1) Left axis deviation and a trend to a horizontal "electrical" position. (2) A deep or very deep Q_3 wave followed by a negative or diphasic T_3. (3) An initial upward deflection in aVL. (4) A significant QaVF wave. (5) A trend to a slight counterclockwise rotation. (6) Occasionally inverted or diphasic T waves in the precordial leads.

These changes are accentuated in the sitting position. Where as the left axis shift is unvariable, the Q_3T_3 pattern occurred only in hearts showing clockwise rotation about the longitudinal axis.

A tentative analysis of the electrophysiological mechanisms involved is offered.

RESUMEN

Un estudio de los trazos electrocardiográficos provocados por el neumoperitoneo en 25 enfermos observados en posiciones de decúbito y sentados, demostró que los cambios, aunque significantes, son exclusivamente por la posición.

En su orden de frecuencia los cambios son: (1) Desviación del eje hacia la izquierda y tendencia a una posición horizontal "eléctrica". (2) Una profunda o muy profunda onda Q_3 seguida de una T_3 difásica o negativa. (3) Una deflexión en aVL hacia arriba. (4) Una onda QaVF significativa. (5) Una tendencia a la rotación en el sentido del reloj. (6) Ocasionalmente ondas T invertidas o difásicas en las precordiales.

Estos cambios se acentúan en la posición sentado. En tanto que la desviación del eje izquierdo es invariable, el aspecto de Q_3T_3, ocurrió sólo en corazones mostrando la rotación en el sentido del reloj alrededor del eje longitudinal.

Se presenta un análisis preliminar de los mecanismos electrofisiológicos que participan en estos cambios.

RESUME

Chez 25 patients porteurs de pneumopéritoine, étudiés en positions couchée et assise, l'électrocardiogramme à montré des changements significatifs, mais d'ordre exclusivement positionnel.

Dans leur ordre de fréquence, les modifications notées sur le tracé pris en position couchée, ont été les suivantes: (1) une déviation de l'axe de QRS vers la gauche, et tendance vers l'horizontalité dela position "électrique". (2) Une onde Q_3 profonde ou très profonde suivie par une onde T_3 négative ou diphasique. (3) Une positivité initiale du complexe ventriculaire en aVL. (4) Une onde QaVF. (5) Une légère tendance vers la rotation antihoraire. (6) Enfin, occasionellement, des ondes T négatives ou diphasiques dans les dérivations précordiales.

Ces modifications deviennent plus marquées sur le tracé enrégistré en position assise. La déviation axiale vers la gauche est constante, tandis que le syndrome électrocardiographique Q_3T_3 apparait uniquement chez les coeurs en rotation horaire autour de leux axe longitudinal.

Après une analyse électrophysiologique détaillée, les auteurs concluent à des changements uniquement positionnels.

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The Diagnosis and Surgical Management of Chylothorax with the Aid of Lipophilic Dyes*

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We wish to present a simple and specific test for chylothorax due to rupture of the thoracic duct in which the patient is fed a fat meal containing a lipophilic coal-tar dye. The dye color becomes grossly detectable in the pleural fluid obtained by thoracentesis a few hours later if the thoracic duct is leaking alimentary chyle. Regardless of the site of rupture, supra-diaphragmatic ligation of the thoracic duct will then prevent further leakage and will cure the patient of the chylothorax.

Chylothorax resulting from traumatic rupture of the thoracic duct is probably not a rare occurrence, yet comparatively few cases have been recorded. Except for a report in 1907 of 31 operative injuries to the duct by DeForest,[1] it has been only during the last few years that surgical damage to the duct has been reported. With more radical neck and posterior mediastinal dissections being done the incidence of surgical trauma to the thoracic duct can be expected to increase. Because so many operative procedures endanger the duct every surgeon should recognize the consequences and know the course to be followed when the thoracic duct is accidentally severed.

Non-traumatic chylothorax, usually following rupture due to neoplastic invasion or mechanical obstruction of the duct, is more common, but the diagnosis seldom is made before autopsy.[2] Because of the gravity of the underlying disease less interest may be shown in diagnosing and surgically correcting the leaking vessel. Even in the presence of mediastinal lymphoblastoma or metastases, however, ligation of the duct may be worthwhile, preventing further depletion of vital fluids, decreasing dyspnea, and freeing the patient of the need for frequent thoracenteses.

Until only a few years ago the feasibility of ligating the duct was not generally accepted, and a spirit of pessimism pervaded all of the case reports of chylothorax. After acknowledging the fact that about half of the patients recover spontaneously without any definitive treatment other than general supportive measures aimed at maintaining nutrition and keeping the chest drained of accumulating fluid by thoracenteses or intercostal tube, surgical possibilities were ignored or were recommended as a last resort. If the duct healed or became occluded the patient survived; if the duct did not eventually close the patient invariably died,—either from inanition or an overwhelming infection which took advantage of his leukopenia and cachexia. As it became apparent through experimental

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work and case reports that transthoracic ligation of the duct is a relatively safe procedure which is curative for chylothorax more interest has developed in diagnosing and actively treating the disease.

Several summarizing reviews have tabulated the recorded cases of traumatic chylothorax. Shackelford and Fisher,[3] reporting two cases in 1938, described 39 earlier cases in detail. They also listed 11 others in which diagnosis was not positively proved. Lampson[4] reported a case treated by transthoracic ligation in 1948 and carefully compiled 17 other reports of traumatic chylothorax in the literature since the series of Shackelford and Fisher. About that same time Holmberg[5] reported four cases, three of which had followed surgical trauma, and Loe[6] reported the deliberate ligation of the duct as a part of the routine radical dissection of the neck. Soon after Baldridge and Lewis[7] and Meade, et al.[8] had reported successful transthoracic ligations of the duct many others[9-13] added individual cases which had been treated surgically. Although the total number reported is still not great it is increasing as the diagnosis of chylothorax becomes more meaningful. Personal communications indicate that many unreported cases exist. The further repetition of such tabulations seems futile, inaccurate, and of questionable value. There is adequate evidence that chylothorax is a serious and often needlessly fatal disease which can be easily diagnosed and can be cured by simple ligation of the thoracic duct.

The value of any curative procedure depends upon proper recognition of the disease. The diagnosis of chylothorax can be very difficult if one depends only on the chemical characteristics and gross appearance of the pleural fluid. Chyle often cannot be identified by the usual methods of fat staining of smears of pleural fluid. Quantitative fat determinations of chylaceous fluids are expensive, usually uninformative, and sometimes misleading. Some of the characteristics of chyle may be simulated in other conditions, such as in a sterile or tuberculous empyema or in a malignancy with pleural or mediastinal extension. Occasionally, as in one of the cases presented in this report, there may be a known mediastinal malignancy with pleural metastases as well as a ruptured duct.

By a simple in-vivo test, such as the ingestion of a dyed fat which is later recoverable from the pleural chyle, many cases can be discovered which might otherwise remain undiagnosed. Not only does this test prove that the pleural fluid is chyle, it also establishes that the thoracic duct fistula is still open and leaking chyle into the pleural space.

The basis of this report is six cases of chylothorax and one of chyloperitoneum in which the diagnosis was made or verified by the use of oral lipophilic dyes. Three of these cases responded favorably to transthoracic ligation of the duct, two closed spontaneously, and the rest, which were not ligated, died. Each of these patients had presented difficulties in diagnosis, and it is doubtful if several would have been recognized without the use of the lipophilic dye test. In addition to these which will be presented, several other cases of suspected chylaceous pleural fluid were differentiated from chylothorax by similar tests. We feel that the incidence of chylothorax is greater than is generally believed,[14] and that the routine

use of this simple dye test in all sterile, turbid, persisting pleural effusions may aid in the discovery of many cases of chylothorax otherwise unrecognizable.

Case 1. Traumatic chylothorax treated by ligation of the thoracic duct: W.J.G., a 52 year old white male taxicab driver, was admitted to the National Naval Medical Center, February 17, 1949. On July 7, 1948, he was in a collision in which his cab rolled over several times. He could recall no specific blow, but had a severe back-ache for several days. Roentgenologic studies showed no fracture or other abnormality. Three weeks after the accident he noticed ease of fatigue and dyspnea. By September he was short of breath, had lost 30 pounds of weight, and had a "tightness" of his chest, low grade fever, and ankle edema. In December he was too dyspneic to work. A cardiologist found cardiac enlargement and electrocardiographic evidence of myocardial damage, and fluoroscopy revealed massive pleural effusion in the right chest. He was hospitalized December 17, 1948—five months after the onset of symptoms. Several thoracenteses were done, each aspiration yielding two liters of cloudy, purulent-appearing fluid. The diagnosis at this time was mediastinal malignancy with pleural metastases. A nodular mass in the anterior abdominal wall further substantiated this impression of metastatic disease; this mass was later biopsied and found to be a benign lipoma. He was given x-ray therapy but continued to lose weight.

At the time of his transfer to the Naval hospital he had lost 97 pounds—his weight having been 287 pounds seven months earlier. A massive hydrothorax was present on the right side, the heart being shifted. Liver was palpable several finger-breaths below the costal margin. Heart rate was 70/minute, with regular rhythm. There were no abnormal neurologic signs. Laboratory studies on admission showed only a moderate leukopenia (5,200 W.B.C./ml.), but this soon declined to a low of 2,000 W.B.C./ml. The erythrocyte count was 3,800,000 with 11 G. hemoglobin. The corrected sedimentation rate was 31 mm./hr. Total protein level was 6.1 G./100 cc., of which albumin was 3.6 G. and globulin was 2.5 G. Bronchoscopy (February 21, 1949) showed no evidence of bronchial tumor. Electrocardiography revealed some diffuse myocardial damage and such other variations as could be explained by the large hydrothorax with mediastinal shift. The patient had been digitalized prior to admission.

When admitted to the hospital he had an ulceration of the buccal mucosa. This developed into an acute glossitis with edema of the mouth floor, necrotic ulceration of the mucosa of the mandible, and erosion of much of the tongue surface. After a week of penicillin (600,000 U. daily) and streptomycin (1 G. daily) the inflammation subsided and the ulcers healed. It was felt that the development of this infection was influenced by the leukopenia and hypoproteinemia. Sternal bone marrow biopsy showed some atypical cells, but no substantiating evidence of neoplastic disease or tuberculosis.

Several transfusions were given. Pleural fluid was removed whenever the patient became dyspneic. Usually the chest taps were at three day intervals, but at times it became necessary to remove fluid daily. A total of 19,260 cc. of chyle was removed.

Sudan III fat stains of this fluid showed microscopic globules of fat to be present, so it was felt that neoplastic erosion of the thoracic duct had occurred. The fluid was invariably alkaline in reaction, about 1.020 in specific gravity, sterile to smear and culture, with an average of 450 leukocytes per ml., of which 98 per cent were lymphocytes. Chloride levels averaged about 1,000 mgm./100 cc. The calcium level was 7.4 mgm./100 cc. The fat content varied, but the average was 2.6 per cent fat. After standing the fluid separated into distinct layers—a top creamy layer above a turbid milky layer, with some particulate sediment at the bottom. Upon agitation with a stirring rod an unctuous butter-like curd could be

churned from the fluid. If a lipophilic dye were present in the fluid,—either by addition in vitro or by ingestion with a fatty meal several hours before thoracentesis—most of the dye color could be extracted and concentrated by this churning, the dye then coloring only the butterlike curd. By this method small amounts of dye not grossly detectable in the whole chyle could be extracted for more quantitative determinations.

Until after this patient had been in the hospital several weeks there had been no indication that this chylothorax was of traumatic origin. Failure to find neoplastic cells in the chest fluid and the comparatively normal appearance of roentgenograms taken immediately after thoracentesis cast doubt upon the admitting diagnosis of carcinomatosis with thoracic duct erosion. Upon further questioning, the patient and his private physician both readily recalled the back injury received in the taxicab collision seven months earlier. All of the symptoms of pleural fluid began about three weeks after the accident, but neither the patient nor his physician had considered this information pertinent because of the latent period between the time of the accident and the onset of the dyspnea.

It was decided to ligate the thoracic duct, inasmuch as there had been no favorable response to the more conservative measures of repeated thoracenteses and low-fat diet. Since Lampson[4] and Meade[8] had reported some difficulties in identifying the thoracic duct branches at the time of ligation, we attempted to color the duct pre-operatively with lipophilic dye. A tube was passed into the duodenum and 100 cc. of melted butter and olive oil containing 500 mgm. of D. and C. Red Number 18 dye was instilled into the duodenum about three hours before surgery (March 1, 1949). The right chest was opened through the eighth rib-bed. About 600 cc. of pink chyle was present in the pleural space. Although several types and colors of lipophilic dyes had been used experimentally during the preceding four weeks, none of the intrathoracic structures were stained or discolored, the colors having remained attached to the fat in the chyle.

The mediastinal pleura was incised posterior to the lateral pulmonary ligament, exposing the anterior surfaces of the bodies of the lower thoracic vertebrae. The main thoracic duct and two smaller branches which joined it several inches above the diaphragm were readily identified. The duct was distended, apparently due to the fatty meal, and was large enough to be palpable through the pleura, so the added precaution of attempting to color the duct was not necessary in this case. The main duct was slightly pink in color, but was not intensely enough colored to assist in its identification. The duct and the two branches were each doubly ligated with black silk ligatures. The duct was not severed. No point of rupture was visible in the duct. Pink colored chyle oozed from the lateral pulmonary ligament just inferior to the inferior pulmonary vein. The lateral ligament was edematous and distorted, and the posterior surface of the ligament had an irregular 2 cm. rent from which the chyle escaped into the pleural space. In reconstructing the history, it seems that the original injury tore the duct, allowing chyle to collect retropleurally within the mediastinum and lateral pulmonary ligament. During this period there was severe back pain, but roentgenograms of the spine showed no fracture and no pleural fluid. After a latent period of two weeks the mediastinal pleura at the base of the lateral ligament tore, allowing the accumulated chyle to flow into the right pleural space, causing symptoms of hydrothorax. In this respect this would resemble the case reported by McNab and Scarlett,[15] who drained a retro-pleural pocket of chyle which, at autopsy, was found to communicate with the pleural space through a similar tear in the lateral ligament.

We had chosen a red dye, which did not give as contrasting a coloration to the duct as a deep green or violet might have given. In the presence of bleeding the pink tinge might have been imperceptible. If the pre-operative ingestion of a lipophilic dye can be of any value in the identification of the ducts for surgical ligation it should be of a color which contrasts with the operative field. Actually,

the pre-operative ingestion of fat to distend the duct is more practical than to attempt to color it as an aid in its identification.

Although chylothorax had been present for at least eight months, with the lung compressed most of this time, there was no visceral pleural cortex or adhesions. The lung was readily inflatable, as had been evident preoperatively in roentgenograms taken after thoracentesis. After ligation of the duct the mediastinal pleura was left open. The lung was re-expanded by positive pressure anesthesia and the chest wall was closed without drainage.

The immediate post-operative course was uneventful and the wound healed. Chest roentgenograms were made twice a week for a month, and at no time was any pleural fluid visible. The liver remained enlarged and tender; the edema of his ankles persisted and became more increased about three weeks after the operation. There was some dyspnea and much weakness upon exertion, but he seemed to improve and gained in weight. His leukopenia disappeared. He was allowed several periods of week-end liberty away from the hospital and was being considered for discharge.

About eight weeks after the operation—on May 14, 1949—he was in the bathroom preparing to leave the hospital when he experienced a sudden sharp pain in his anterior chest. He clutched at his chest and fell to the floor unconscious. He was pronounced dead a few minutes later. Autopsy showed a small amount of clear fluid in the right pleural space. The black silk ligatures were still effectively occluding the duct, which was not distended or ruptured below the ligation. No point of rupture could be identified anywhere along the course of the duct. The immediate cause of death was attributed to myocardial failure. No evidence of coronary thrombosis was found. All of the visceral organs showed diffuse collagenous changes resembling lupus erythematosis. The walls of the thoracic duct had marked hyalinization, as did the walls of all of the large intrathoracic blood vessels. Whether such changes occurred because of the prolonged chylothorax or duct ligation, or whether the changes were present before the accident, predisposing the duct to rupture, was not determinable. Lupus erythematosis had never been suspected in this man. It is believed that the weakened duct ruptured more easily because of the diffuse collagenous disease of its wall. A similar correlation of these two diseases is suggested by a case discussed by Scannell.[13]

Case 2. Non-traumatic chylothorax without ligation: F.M., a 60 year old negro, was admitted to the National Naval Medical Center on January 5, 1949, because of dyspnea of three weeks duration. He had a history of 15 years of hypertension (196/110) and of an egg-sized mass in the left side of his neck for two years. Examination at the time of admission revealed an 8 x 5 cm. nodule medial to the left sternocleidomastoid muscle and several other large firm nodes in the submaxillary, axillary, and inguinal areas. The trachea was deviated by the cervical mass. The left chest film was flat to percussion and breath sounds were absent. The liver was enlarged and nodular, and there was marked dependent edema of the lower extremities.

The initial hemogram showed 3,400,000 R.B.C., 10.5 G. of hemoglobin, and 8,300 W.B.C. per cu. mm. The corrected sedimentation rate was 17 mm. per hour. Total proteins were 7.9 G./100 cc., of which albumin was 4.3 G. and globulin was 2.7 G.

Roentgen examination revealed a massive left hydrothorax with mediastinal displacement. Thoracentesis removed 1,500 cc. of clear straw-colored fluid, which contained no malignant cells or bacteria. This fluid was not chylous in appearance, and no fat test was done.

An electrocardiogram indicated myocardial damage of the left ventricular strain pattern. After the withdrawal of 200 cc. of the same clear amber fluid the patient showed signs of peripheral vascular shock and anterior chest pain, so the needle was removed. Nine days after this the chest was again tapped and 615 cc. of thick creamy fluid was obtained from approximately the same site of thoracentesis.

This fluid was entirely different from the previous samples. This had the gross appearance of pus but was sterile. Smears showed no malignant cells or acid-fast bacteria. Fluid reaccumulated rather steadily. A week later about 1,500 cc. of similar fluid was removed. Microscopic examination after staining with Sudan III showed fat globules to be present. A cervical lymph node was removed. All of the normal structures of the node had been replaced by malignant cells, which invaded the adjacent fatty tissue as well. The cell type was that of small lymphocytes with round hyperchromatic nuclei and scant cytoplasm. Mitotic figures were infrequent.

A bronchoscopic examination revealed no tumor or other bronchial disease, but the carinal angle was distorted by a mediastinal mass. Bronchial washings showed no malignant cells. He was given x-ray therapy (2,775 Roentgen units) over the mediastinum and two courses of nitrogen-mustard (methyl-bis B-chloroethylamine), receiving 0.1 mgm. of nitrogen-mustard for each kilogram of body weight on eight consecutive days.

Thoracentesis had to be repeated at least once a week, removing from one to three liters of chyle each time. This fluid had a specific gravity of 1.018, was always alkaline in reaction, and, upon standing, would separate into distinct layers. The laboratory analysis of a typical sample of this chyle is shown in Table II. In a five month period over 35,000 cc. was removed. For several weeks

TABLE I

ANALYSIS OF TYPICAL SPECIMEN OF CHYLE FROM CASE 1 (W.J.G.)

Gross appearance: 1,000 cc. turbid gray fluid, separating into three distinct layers on standing.

Reaction: alkaline.
Specific gravity: 1.020.
Chlorides: 1,000 mgm./100 cc.
Calcium: 7.4 mgm./100 cc.
Phosphorus: 1.8 mgm./100 cc.
Total fats: 5,200 mgm./100 cc.
Bacteriology: sterile to culture.
Cell count: 450 W.B.C./ml.
Differential cell count:
Lymphocytes 97 per cent.
Neutrophiles 2 per cent.
Plasma cells 1 per cent.
Total protein: 6.1 Grams/100 cc. (Albumen 3.6 G.; Globulin 2.5 G.).

TABLE II

ANALYSIS OF TYPICAL SPECIMEN OF CHYLE FROM CASE 2 (F.M.)

Gross appearance: 2,000 cc. cloudy pink-gray fluid.

Reaction: alkaline.
Specific gravity: 1.018.
Chlorides: 646 mgm./100 cc.
Calcium: 7.8 mgm./100 cc.
Phosphorus: 1.9 mgm./100 cc.
Non-protein nitrogen: 45 mgm./100 cc.
Total fats: 5,640 mgm./100 cc.
Bacteriology: sterile to culture.
Cell count: 1,400 W.B.C./ml.
6,125 R.B.C./ml.
Differential cell count:
Lymphocytes 89 per cent.
Neutrophiles 4 per cent.
Eosinophiles 6 per cent.
Plasma cells 1 per cent.
(Soaps 0.08 per cent. Free fatty acids 0.07 per cent. Neutral fat 2.57 per cent).
Total protein: 3.1 Grams/100 cc. (Albumen 2.0 G.; Globulin 1.1 G.).

after the x-ray therapy and the nitrogen-mustard treatments he showed clinical improvement and felt stronger, but this was only a temporary phase and he soon resumed the decline. Dyspnea was relieved immediately after each thoracentesis. Sometimes the dyspnea returned after a few hours, but occasionally it was relieved for several days. The greatest relief was obtained by restricting the diet to eliminate fats. Supra-diaphragmatic ligation of the thoracic duct was considered

as a palliative measure—both to relieve his dyspnea and to conserve body proteins and fats—but his general debility and cardiac status was such as to preclude any major surgical procedure. He died June 10, 1949. Autopsy showed extensive small-cell lymphosarcoma. The mediastinal nodes were completely replaced by malignant masses which involved the thoracic duct for almost its entire length.

Since this patient needed many thoracenteses, we were able to test the relative merits of several lipophilic dyes as an aid to the diagnosis of chylothorax. He ate the dyes in a jam-like mixture of dye and butter spread thickly on crackers or over ice cream. He appeared to have no objection to this, even when the "jam" was green or violet. Usually the dye appeared in the thoracic fluid within four hours.

Case 3. Chylothorax due to mediastinal Hodgkins disease—treated successfully by transthoracic ligation of the duct: R.B., a 56 year old white woman, had recently had lobar pneumonia of her left lower lobe which was effectively treated with antibiotics. During this illness she had violent straining coughing spells. During one of these episodes she experienced a sharp excruciating pain in her back which was so persistent that a chest x-ray film was taken the next day. This showed clearing of the left sided pneumonia, a normal right chest, but a widened mediastinum. The pain subsided and she was discharged, but two weeks later she suddenly became dyspneic. A roentgenogram showed pleural effusion of the right side—the opposite side from that involved in the pneumonic process. Thoracentesis (November 4, 1950) yielded 2,600 cc. of tan turbid fluid which looked like coffee with cream. Fluid rapidly re-accumulated, and she was tapped at five-day intervals. The fluid was sterile. Microscopic examination showed many lymphocytes. Sudan III stains of the centrifuged sediment showed a few globules which stained red, but it was not considered conclusive proof of chylothorax by the pathologist.

A supraclavicular node biopsy then established the diagnosis of Hodgkin's disease. Since the thoracic duct is often eroded by such mediastinal malignancy, it was felt that the duct had probably been infiltrated and weakened by the malignancy, but had not ruptured until the trauma of coughing caused it to leak retropleurally. Later this fluid broke into the right pleural space.

The lipophilic dye test was used to substantiate this. She was given a sandwich containing one gram of D. and C. Green Number 6 dye mixed in a quarter of a pound of oleomargarine. The following morning 850 cc. of green-tinted milky fluid was aspirated from her right chest. Churning the fluid with a glass rod caused a deeper green butter-like curd to collect on the rod. A sample of this chyle was mixed with ether, causing the dye to be extracted into a green ether layer. We repeated the test, using a red and later a violet dye, with the same positive results.

On December 8, 1950 her thoracic duct was ligated just above the right diaphragm. A small segment of duct removed for histologic study showed no abnormality. The lung expanded promptly after surgery, and no drainage was used. She was kept on a low fat diet for several weeks as an added precaution. The chest remained clear, and she was discharged 10 days after ligation. She regained strength rapidly and returned to work as a librarian three weeks after leaving the hospital. She was able to eat fats without discomfort.

This patient is still alive and able to work, now more than two years since ligation of her thoracic duct. X-ray therapy and nitrogen-mustard treatments have been beneficial, but she is now showing symptoms of advancing malignancy. She will undoubtedly die of this—but it is just as certain that she would have died two years ago if the duct had not been ligated. Had the diagnosis of chylothorax not been established her death would have been credited to the mediastinal and pleural manifestations of the malignant disease, and even an autopsy could not have proved otherwise.

Case 4. Non-traumatic chylothorax with spontaneous healing of eroded duct: E.W., a 61 year old white man, had had a carcinoma of the prostate removed in 1947, followed by x-ray irradiation and hormone therapy. Two years later he developed dyspnea, generalized weakness, and 40 pounds loss of weight. Ankles and liver were enlarged, and he appeared to be in congestive heart failure. A roentgenogram showed a right hydro-thorax. A large supraclavicular node was removed. This revealed carcinomatous metastasis, presumably from the earlier prostatic malignancy.

Thoracentesis (September 22, 1949) yielded 2,500 cc. of thin gray-green milky fluid, thought to be empyema pus until all cultures were sterile. Microscopic studies of the fluid revealed many small round cells, actually lymphocytes but not distinguishable from neoplastic cells. The pleural fluid reaccummulated rapidly, but roentgenograms taken immediately after thoracentesis showed complete re-expansion of the lung and a widened mediastinum.

He was given a fat meal of butter containing one gram of the lipophilic dye, D. and C Green Number 6. Two days later 1,800 cc. of pastel-green milky fluid was aspirated from his pleura. Green dye was extracted from this fluid by ether. The ether extraction seemed important in this case because the original color of the fluid had been slightly greenish. The test was later repeated several times using D. and C. Red Number 18, which gave a pink color.

The patient refused surgery, and in view of the dismal outlook of his metastatic disease we did not urge surgical ligation of the duct as strongly as we now wish we had. He received stilbestrol, x-ray therapy, and repeated thoracentesis. Gradually the periods between chest taps became shorter, dyspnea re-appearing only three or four days after thoracentesis. By restricting his fat and fluid intake a week between chest taps could be tolerated. His blood protein level was supported by oral protein hydrolysate and occasional blood transfusions.

In spite of the proved metastasis to his neck and presumably to his mediastinum, with continued loss of body fluids, this man lived for two years. After a year of weekly chest taps the amount of fluid gradually decreased, and 15 months after the onset of chylothorax the duct apparently sealed off spontaneously. As the chyle leakage diminished, it became less cellular and the fat content dropped to 2.1 G./100 cc. from its former level of 4.6 G./100 cc.

Although this patient survived and eventually sealed off the ruptured duct, there is little justification of such expectant treatment. During the 15 months period of waiting for spontaneous healing a total of 126,000 cc. of chyle was removed in 90 thoracenteses. The amount of fat and protein lost to his body in this 33 gallons of chyle was out of all proportion to any risk he would have undertaken with supradiaphragmatic ligation of the thoracic duct. Eventually he succumbed to the malignancy which had caused the chylothorax, but he would have been much more comfortable for many months if we had disregarded his basic disease and ligated the thoracic duct as a palliative measure.

Case 5. Non-traumatic chylothorax due to malignancy: E.A., a 56 year old white woman, had lymphosarcoma with mediastinal and cervical metastases, a cervical node biopsy having established the diagnosis. Pleural fluid was present on the right. Thoracentesis (April 21, 1950) removed 2,000 cc. of turbid gray-brown fluid, alkaline in reaction and sterile to culture. The fluid re-accumulated rapidly. Lipophilic dye (D. and C. Green Number 6) was fed in butter; thoracentesis on the following day showed green dye in the fluid. Her family, aware of the lymphosarcoma diagnosis, refused to allow palliative ligation of the thoracic duct. By adhering to a non-fat diet the pleural fluid was reduced in volume from 2,700 cc. to 800 cc. in weekly thoracenteses. During her terminal five months illness 28 liters of chyle were removed. Ligation of the duct would probably not have altered her decline, but it could have eliminated the discomfort of the fluid and the repeated chest taps.

Case 6. Traumatic chylothorax with ligation of thoracic duct: R.B., a 32 year old colored man, was admitted to the hospital because of shortness of breath. Onset had been gradual, and he had been treated as cardiac decompensation in an out-patient clinic. X-ray studies revealed the left hemithorax filled with fluid. Thoracentesis removed 1,500 cc. of white milky fluid. Examination of the left side of the neck for nodes revealed a healed knife wound which had been received about three months before. He recalled that the wound had wept white watery "pus" for about two weeks before closing. His shortness of breath began soon afterward.

The fluid re-accumulated after its removal. The lipophilic dye test proved it to be alimentary chyle. Rather than to reopen the knife wound in a futile attempt to find the source of the leak, it was decided to ligate the thoracic duct just above the right diaphragm. A short intercostal incision was made on the right side after thoracentesis had evacuated all of the free fluid from the left pleural space. The duct was ligated with silk. Recovery was uneventful and no more fluid formed.

Case 7. Non-traumatic chyloperitoneum with spontaneous healing of eroded cysterna chyli: A.G.L., a 72 year old white female, developed ascitis and other evidences of congestive cardiac failure in November, 1952. Abdominal paracentesis yielded 2,000 cc. of turbid milky white fluid. Because this was chylaceous, the green lipophilic dye test was used to determine whether this was chyle. The paracentesis done on the following day showed a decidedly green color in the peritoneal fluid. The test, repeated at a later date with a red dye, again showed gross discoloration from the dye, indicating a rupture of the thoracic duct or cysterna chyle below the diaphragm.

She was placed on a fat free diet and fluids were restricted for several weeks. The ascitic fluid decreased and after seven aspirations, a total of 12,000 cc. of fluid, no more peritoneal chyle collected, the ruptured cysterna chyle having sealed itself off. The patient is still alive but bed-ridden.

The cause of this chyloperitoneum was probably due to erosion of the duct by metastatic neoplastic disease. An enlarged nodular liver is present, and there is a history of an ovarian malignancy having been removed 10 years before. Here again the outlook is poor, but the distressing symptoms of chyloperitoneum are no longer present and the patient is consequently more comfortable, regardless of her ultimate prognosis.

Case 8. Pseudo-chylothorax—Chylaceous fluid from pleural diseases: J.L., a 67 year old white male, had recently recovered from an acute pneumonic infection for which he had received large doses of penicillin. An x-ray film made at the onset of his illness showed a typical lobar consolidation, but most of his chemotherapeutic treatment had been carried on at home so follow-up x-rays were not available. After the febrile symptoms had subsided there was continued weakness, shortness of breath, and clinical signs of pleural fluid. He was hospitalized and found to have his entire right chest filled with fluid. Thoracentesis removed 2,200 cc. of thick creamy coffee-colored fluid. Because this fluid was sterile to culture and re-accumulated rapidly after chest tap a presumptive diagnosis of chylothorax was made. Sudan III fat stains of the fluid were equivocal, the pathologist finding a few globules of fat scattered throughout the fluid, but not enough to warrant a diagnosis of chylothorax. Lipophilic dye was then fed to this patient. Subsequent thoracentesis failed to show any gross evidence of the color, and the color could not be extracted with ether or by churning the fluid. Repeating the test with a different color of dye gave the same negative result. After several taps the fluid decreased and then disappeared.

This patient, having been treated with antibiotics for a pneumonic infection just prior to the hydrothorax, probably had a sterilized empyema. This case is included because it illustrates a negative response in a "pseudo" chylothorax where no rupture of the thoracic duct existed.

Several similar cases of pleural fluid which was due to neoplastic pleural metastases have given similar negative results to the lipophilic dye test.

Anatomical and Physiological Considerations

The thoracic duct originates in the cysterna chyle, a retroperitoneal lymphatic collecting chamber anterior to the second lumbar vertebra. It enters the chest through the aortic hiatus of the diaphragm between the aorta and the azygos vein, passing upward in close proximity to the vein and usually with demonstrable branches running into the vein. The duct runs along the right side of the vertebral bodies to the fifth thoracic vertebra where it crosses the midline to pass behind the arch of the aorta and empty into the left subclavian vein near its juncture with the internal jugular vein. Lee[16] and Davis[17] have described numerous anatomical variations ranging from completely double ducts to a branching plexus of communicating lymph channels entirely below the diaphragm. The variations are so common that the classical description of the duct as a single vessel throughout its entire course is seldom encountered. Often the termination is delta-like, and sometimes several of the branches terminate in other veins than the left subclavian, such as the azygos, the right subclavian, or one of the jugulars. Lowman and his associates[18] have demonstrated some of these variations roentgenologically by injecting the ducts with radio-opaque dyes.

Such variations of the duct would make it difficult to find the site of a rupture even at autopsy. In general, a right chylothorax usually results from a rupture of the duct below the level of the fifth thoracic vertebra, whereas a left chylothorax might indicate an injury at a higher level. Because of the difficulty in exposing the lower part of the duct from the left chest it seems desirable to ligate the duct by a right sided approach, regardless of the location of the chylothorax. The chyle can be removed by thoracentesis if it happens to be on the left side. On the other hand, Meade[8] has reported a case in which the left lung would not re-expand and a decortication was necessary. In this patient a left sided approach was preferable. In order to reach the thoracic duct the aorta was freed and lifted anteriorly, allowing access to the duct for ligation. In such a procedure the identification of the duct and its branches can be very difficult. In the cases which we have seen there has been no failure of prompt re-expansion of the lung, as evidenced by roentgenograms taken immediately after a thoracentesis.

By ligating the thoracic ducts of experimental animals, Lee[19] demonstrated the remarkable tendency of these lymphatic channels to develop collateral systems. Connections to the inferior vena cava, intercostal vessels, lumbar veins, and even the renal and mesenteric veins are reported. This capacity to form collateral routes is so strong that it is difficult to produce a complete block. Blalock[20] was able to obtain complete blockage of this lymphatic system in only three dogs after 267 operative attempts.

Following experimental ligation of the thoracic duct there is no demonstrable nutritional disturbance. Blood fat levels decrease immediately but

return to normal within two or three weeks.[21] The circulating lymphocytes also decrease 50 per cent after ligation, but return to normal in a few weeks. There is certainly much less physiologic upset with ligation than with complete severance and chylothorax. The organism adapts to a ligated duct, but cannot tolerate the constant loss of chyle from an open duct fistula. It is difficult to understand the reluctance with which elective ligation of the duct has been approached in the past. It seems to be a relatively harmless procedure,—certainly fraught with no greater dangers than ligation of any of the great veins,—and is curative for an otherwise fatal disease.

Chyle differs from serum in that there is a smaller amount of protein but a much larger amount of fat. It contains fibrinogen and prothrombin, but is low in thromboplastin and contains no platelets. There is a hemolytic action due to the soaps and fatty acids, but rapid dilution in the blood stream prevents actual hemolysis. Freeman and Johnson[22] have reported that direct anastamosis of the lower thoracic duct to the portal vein causes appreciable hemolysis in the circulating blood. Lampson[4] showed that chyle is bacteriostatic but not bacteriocidal. Florer and Ochsner,[23] in comparing chyle and "pseudo-chyle," say that true chyle always has a specific gravity above 1.012 and there is usually from 0.4 to 4.0 Grams of total fat in each 100 cc. Other fluids which may resemble chyle have a lower specific gravity and usually less than 0.3 Grams of fat in 100 cc. Quantitative fat studies are difficult to obtain and specific gravity can be unreliable, so these points are often of little use in differentiating. The selective affinity of certain coal-tar dyes for fats is a much more reliable test, either when used as a tracer, as in our cases, or as a stain for the microscopic examination for fat globules.

Following rupture of the thoracic duct and leakage of chyle into the mediastinum there is a latent period of several hours or even several weeks before symptoms of pleural fluid appear. This may be noted in the first three cases presented in this report. The escaped chyle collects retropleurally in a comparatively small closed space. Undoubtedly many ruptures of the duct seal off at this stage and never develop into a recognizable pleural chylothorax. It is only when the fluid pressure is great enough to cause a second rupture,—that of the pleura,—that chylothorax becomes apparent. This second point of rupture is usually in the lateral pulmonary ligament. Any attempt at suturing or closing off this secondary tear would be valueless for it might be a considerable distance from the leaking duct.

The break-through into the pleural space may be sudden,—sometimes with shock and circulatory collapse. Usually the condition is manifest only by pressure symptoms due to the accumulating pleural fluid which compresses the lung.

The dyspnea of chylothorax may be readily controlled by repeated thoracenteses. The continued loss of chyle, however, produces a second set of symptoms due to the depletion of essential body elements. Weakness, increased thirst and hunger with progressive apathy and inanition, peripheral edema and emacination due to hypoproteinemia follow.

Oeken,[24] in 1904, and later Bauersfeld,[25] Schnug,[26] and others[23,27] reported beneficial effects from the intravenous re-administration of aspirated chyle. Several unexplained sudden deaths with "anaphylactoid" reactions have occurred[28,29] during such procedures, so the re-administration of chyle has become generally abandoned in favor of surgical ligation of the duct.

Lipophilic Dyes in Chylothorax

If so definitive a procedure as the elective ligation of the thoracic duct is to be advocated in every case of chylothorax there is need for a simple test which unequivocally will establish the diagnosis of a ruptured thoracic duct. A fat soluble, non-toxic dye which can be ingested with a fatty meal then later recovered from the pleural chyle seems to meet this need, being simple, safe, cheap, and reasonably specific.

In 1929 Fletcher and Harrison[30] used a lipophilic dye to diagnose a case of chylurea in a 17 year old girl with a fistula due to chronic tuberculous peritonitis. They gave her 100 mgm. of Sudan III dye orally, recovering the dye color from the urine by ether extraction. Crandall, Barker and Graham[31] gave 250 mgm. of Sudan III in 50 cc. of olive oil to a patient with a cervical chylous fistula. The color first appeared from the fistulous opening in 87 minutes. Color intensity increased for the next three hours. Pisek[32] gave 7½ G. of Sudan III orally to a nine week old infant suspected of having chylothorax after a severe convulsive seizure. Thoracentesis later showed a pink tinge to the milky fluid, apparently confirming the diagnosis, although no attempt was made to extract or concentrate the dye. Spontaneous cure occurred. Since a small amount of blood can give the same pink color, we feel that it is desirable to use a green or violet color instead of a red dye.

Water soluble dyes, such as trypan blue, have been used in experimental duct fistulae to study the rate of flow and absorption of chyle,[33] but such dyes are valueless in diagnosing chylothorax because they are not specific for fat or chyle and can be recovered from non-chylous pleural effusions. A lipophilic dye which is held securely by the fat portion of the chyle is specific,—and when it is recovered by thoracentesis after the ingestion of the stained fat indicates a ruptured thoracic duct.

Vegetal dyes, such as annatto, the coloring material in oleomargarine, are of no value because the dye is destroyed in the stomach and none of the color is passed into the chyle. We fed 500 mgm. of annatto in butter to two of our patients and could recover none of the color in the pleural chyle.

Sudan III and Sudan IV are well known laboratory dyes which can be used for fat staining of chyle in-vitro,—but they present certain disadvantages for ingestion. Being red in color they can be confused with blood in the pleural fluid unless one extracts the dye with ether or does a microscopic examination for stained fat globules. The Sudan dyes do not concentrate well, so that it is not as easy to detect the pink tint as it is with some of the darker staining dyes. The Sudan dyes also are not ap-

proved for use as a drug or cosmetic ingredient because of chemical impurities which might be toxic.

The Cosmetic division of the Pure Food and Drug Administration furnished and checked the toxicity of the lipophilic dyes we used. The dyes which gave the best concentrations in chyle were coal-tar dyes with the commercial designations of D. and C. Red Number 17, D. and C. Red Number 18, and D. and C. Green Number 6. The D. and C. (Drug and Cosmetic) is a standard form of nomenclature indicating their acceptability for use in drugs or cosmetics. These red dyes are commonly encountered in lipsticks. All of these dyes are readily obtainable, cost but a few cents a pound, and are non-toxic in doses as large as one gram daily. Because of the better contrast of color, D. and C. Green Number 6 would seem to be the most preferred of the dyes we used.

In preparing the dye for ingestion a gram of the dye was mixed with a quarter pound of butter or oleomargarine. For pre-operative use, or in children or experimental animals, the dye can be given in olive oil through a Levine tube. The dyed butter is spread very thickly on bread or it can be eaten over ice cream. The taste is not unpleasant, tasting only of the butter,—but the appearance is startling and not especially appetizing,—the concentrated dye making the unction almost black in color. The red dye resembles a jam,—but the green or violet dyes seem more palatable when served as a sandwich,—preferably in the dark! When eaten in the dark the patient tastes only the butter. We encountered no difficulty in inducing our patients to eat the dyed fat. The dye is not effective if taken in a capsule. It is necessary to stir the powder into the fat for intimate contact for maximal concentration of the color in the pleural chyle.

Thoracentesis is done on the following morning. If there has been leakage of alimentary chyle into the pleural space the aspirated fluid will be grossly discolored by the dye. Adding a small amount of alkali to the colored chyle further intensifies the color. Mixing ether with the alkalinized chyle causes the color to be extracted into the ether layer.

Churning the collected chyle with a stirring rod is the quickest and easiest way of concentrating the color in those cases where there is any doubt of the gross appearance of the chyle. After a few minutes of churning the stained fat collects on the rod as a butter-like unctuous curd. Small amounts of dye not grossly detectable in a large amount of chyle can be concentrated in this manner. In none of our cases, however, was such extraction necessary to identify the color grossly.

The Surgical Management of Chylothorax

Surgical ligation of the thoracic duct is becoming accepted as a feasible operation which is curative for chylothorax. As long ago as 1898 Cushing[34] sutured the duct after its surgical damage. In 1906 Bockenheimer[35] described suturing and tamponade of a duct which had been injured during the sawing of a clavicle. J. B. Murphy[36] in 1911 quoted Jonnesco as having occasionally resorted to the deliberate ligation of the duct to control the spread of abdominal cancers. In 1922 Costain[37] attempted to show that

there was fatal absorption of toxic materials via the thoracic duct in diffuse septic peritonitis,—and in the following years he popularized lymphaticostomy, the purposeful production of a cervical thoracic duct fistula, as a treatment for peritonitis. In this operation the duct was exposed in the left neck, ligated near the subclavian vein, then slit longitudinally so that chyle drained from the fistula. Several survivors of this[38-40] procedure were reported by Costain. He did not prove that duct ligation helped the peritonitis,—but did show that these fistulae usually closed spontaneously in a few days with no ill effects to the patients. Cooke,[41] in reporting a case which recovered after such a lymphaticostomy, concluded that the duct fistula had nothing to do with the recovery since there was little or no flow of chyle in these dehydrated and starved patients with peritonitis. His second conclusion was that the cervical thoracic duct is most difficult to find.

Elective thoracotomy for the supra-diaphragmatic ligation of the thoracic duct has long been condemned, yet it seems to be a comparatively benign procedure which is curative for an otherwise fatal disease. This discrepancy is due to the fact that repair of the leak has erroneously been associated with the idea of mediastinal dissection and repair of the site of rupture. Recently Effler,[42] advocating conservative closed intercostal drainage in a case of a surgically damaged duct, stated that mediastinal exploration in such cases is dangerous and finding the leaking point might be impossible because of its inaccessibility. Actually there is no need to explore the mediastinum and we have not advocated it. The duct is a one-way vessel with competent valves and can be ligated at its most exposed portion just above the diaphragm. There is no need to expose the leak.

If the duct is cut during surgery and the condition is recognized the duct can be ligated or sealed off with a Gelfoam tamponade. Smithwick has been quoted[7] as having cut the duct a score of times, yet had only one resulting chylothorax. When a chylothorax does result, either of traumatic or non-traumatic cause, the duct can best be ligated through the right chest at the point where the duct lies exposed over the anterior surfaces of the vertebral bodies. The optimal time for ligation is probably at that time when it becomes apparent that the duct is not sealing off spontaneously. If there is progressively less chyle each time the chest is tapped there may not be a need for ligation. If, on the other hand, there is no diminution in the pleural fluid after several taps it may be apparent that surgical ligation will prevent further loss of body fluids and be desirable to ligate the duct relatively early.

Since having become interested in this problem we have been routinely exposing the lower thoracic duct in all cases of right-sided thoracotomies encountered during the past two years. Several double ducts were seen, and in all cases it was possible to identify the thoracic duct. In 14 cases of far advanced unresectable bronchogenic carcinoma which had exploratory thoracotomies the thoracic duct was ligated, a detailed report of

which will be published later. In none of these cases were there any untoward post-operative symptoms indicating duct obstruction. Such patients are usually on a low fat diet for several days post-operatively following any major surgery, so few of them showed any effect of the ligation. In one case death from other causes was too early to allow any inferences from the procedure. Five of the remaining cases had autopsies in from four to 20 weeks after the exploratory surgery and duct ligation. These patients still had the silk ligatures in place, and accessory channels connecting to the azygos system were demonstrable in three of the patients. In one man who died nine weeks after surgery no demonstrable collaterals could be found, yet he had not experienced abdominal cramping or any other symptoms referable to the thoracic duct. In none of these cases was there any distension of the lower duct distal to the ligatures. This, however, may have been conditioned by the cachectic manner in which most of such cases terminate.

The dyes used in this study were provided by the Color Certification Branch of the Food and Drug Administration, Federal Security Agency, Washington 25, D. C., and we wish to thank them for their cooperation and advice. The dyes may be obtained in any quantities from the following manufacturers: Pylam Products, Inc., 799 Greenwich St., New York 14, N. Y.; National Aniline Division of Allied Chemical and Dye Corp., 40 Rector St., New York 6, N. Y.; H. Kohnstam Co., 87 Park Place, New York, N. Y.

SUMMARY

A simple and effective means of diagnosing chylothorax is presented. When thoracentesis is done several hours after the patient has eaten a fat meal containing lipophilic dye the color of the dye can be identified in the pleural fluid if the thoracic duct is ruptured. This test not only identifies the pleural fluid as being alimentary chyle but also establishes the fact that the thoracic duct is still leaking. The test described is simple, safe, cheap, and specific, and should be used in all cases of turbid, sterile, alkaline pleural fluid which tends to recur after removal by thoracentesis.

Chylothorax resulting from a rupture of the thoracic duct is a serious and often fatal condition characterized by respiratory embarrassment and inanition. The conservative management of persisting chylothorax is unsatisfactory. Although repeated chest taps or intercostal drainage and subsistence on a fat-free diet may result in spontaneous cure, the mortality in such cases has been reported to be over 50 per cent. All those ducts which do not seal off lead to a fatal termination. Huge amounts of valuable body foods and fluids will be lost while awaiting spontaneous cure. Ligation of the thoracic duct is a feasible procedure which is curative for chylothorax resulting from operative or traumatic injuries to the duct. Even when the chylothorax is a result of neoplastic invasion of mediastinal structures ligation of the duct will eliminate a most uncomfortable complication. The patient tolerates ligation of the thoracic duct far more readily than he does its section and the continued loss of chyle.

RESUMEN

Se presenta un recurso efectivo y sencillo para el diagnóstico del quilotórax. Cuando se hace una toracentesis a un enfermo varias horas después de que ha tomado una comida rica en grasa que contiene un colorante lipofílico, ese colorante puede identificarse en el líquido pleural si el conducto torácico está abierto. Esta prueba no sólo identifica el quilo en el líquido pleural sino establece el hecho cuando el conducto está todavía rezumando. La prueba descrita es sencilla, segura, barata y específica y debe usarse en todos los casos de líquido pleural turbio, estéril, alcalino que tiende a volverse a formar después de extracción.

El quilotórax que resulta de una ruptura del conducto torácico es una complicación seria y a menudo fatal, que se caracteriza por el impedimento respiratorio y la inanición. El tratamiento conservador del quilótorax persistente no es satisfactorio.

Aunque las punciones repetidas pueden conducir a la curación, así como el drenaje intercostal, y la privación de alimentos ricos en grasa, la mortalidad en tales casos se ha referido como de 50 por ciento.

Todos esos conductos que no se clausuran conducen a un término fatal. Enormes cantidades de alimentos valiosos para el organismo se pierden mientras se espera la curación espontánea. La ligadura del conducto torácico es practicable y se curativa de las ruturas del mismo producida quirúrgicamente.

Aún cuando el quilotórax es resultado de invasión neoplásica de los órganos mediastinales, la ligadura del conducto eliminará esa complicación tan incómoda. El enfermo tolera la ligadura más facilmente que lo que tolera la sección del conducto y la continua pérdida de quilo.

RESUME

Les auteurs présentent un moyen simple et efficace de diagnostic du chylothorax. On pratique une ponction pleurale que ques heures après que le malade ait fait un repas riche en graisses contenant un produit colorant s'y fixant électivement. La couleur se retrouve dans le liquide pleural, s'il y à rupture du canal thoracique. Ce procédé non seulement donne la preuve que le liquide pleural est bien du chyle alimentaire, mais il démontre en outre que le canal thoracique est encore perforé. Il est simple, sûr, non onéreux, et spécifique. Il devrait être utilisé dans tous les cas où le liquide pleural trouble, stérile, et alcalin, à tendance à se reproduire après avoir été vidé par thoracenthèse.

Le chylothorax qui résulte de la rupture du canal thoracique, est une affection grave et souvent fatale. Elle entraine des troubles respiratoires, et une dénutrition progressive. Le traitement conservateur d'un chylothorax persistant n'est pas satisfaisant. Sans doute, on peut obtenir une résolution spontanée par des ponctions répétées ou par un drainage inter-costal, et par un régime dépourvu de graisses. Toutefois; dans une telle éventualité, la mortalité reste supérieure à 50%. Dans tous les cas où le canal thoracique ne s'oblitère pas, l'évolution est fatale. En attendant la guérison spontanée,

il se perd de grandes quantités de liquide et d'éléments nécessaires à l'organisme. La ligature du canal thoracique est un procédé qui permet la guérison dans les cas de chylothorax consécutifs à une lésion opératoire ou traumatique du canal. Même lorsque le chylothorax est consécutif à l'invasion cancéreuse du médiastin, grâce à la ligature du canal on peut éviter une complication extrêmement pénible. Le malade supporte beaucoup mieux la ligature du canal thoracique que la perte continuelle du chyle consécutive à sa section.

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Degenerative Lung Disease*

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Degenerative lung disease includes diffuse hypertrophic emphysema, bullous emphysema, and "vanishing" or "cotton-candy" lung. It is the author's concept that all of the above clinical entities are stages of one disease with a common etiological factor, namely obliterative vascular disease of both the bronchial and pulmonary systems. It is thought that this vascular disease starts in the bronchial arterial system, which, through its ramifications, influences the pulmonary arterial system through the vasa vasorum. The lack of nutrient blood supply first causes destruction of the elastic fibers with resultant fibrosis in the alveolar spaces. With the increasing loss of nutrient blood supply, this destructive process may progress until the main lobar bronchi and vessels have been destroyed. All stages of lung destruction may exist at the same time in the same lung.

Our concept of the vascular pathogenesis of pulmonary emphysema arose from observations made prior to 1949 during surgery on emphysematous patients who were being operated for other disease, such as carcinoma, bronchiectasis, etc. In some instances, emphysema was unexpectedly encountered at operation. It was noted that in areas of degenerated or bullous disease there was a paucity or absence of bleeding. These areas represented actual destruction of lung parenchyma—not simply pleural or superficial parenchymal changes although such was suggested by their protrusion above the surface of the lung. There was a gradation from the gross changes of hypertrophic emphysema to complete degeneration of a segment or lobe suggesting that this was the same disease in various stages. Under intratracheal anesthesia these emphysematous lungs, especially the destroyed areas, filled readily with air but expiration was difficult because of the loss of lung elasticity.

The clinical entity of degenerative lung disease does not include compensatory emphysema, the trapping of air behind a foreign body, bronchospasm as seen in asthma, pulmonary cysts, or subpleural blebs.

In blebs, tension results from the mechanical trapping of air[18] with secondary compression of normal lung tissue between the chest wall and the hilum. This differs from bullae in which there is an absence of tension. Bullae involve lung parenchyma, and are associated with hypertrophic emphysema.[27] Blebs compress adjacent lung tissue because of the positive pressure within them, whereas bullae have bronchial pressures, negative or positive depending upon the phase of respiration, and they progressively enlarge because of their inelastic nature and may gradually stretch with respiration until they fill the chest cavity ("stretched cysts").[19] Tension blebs may also become large enough to fill a hemithorax. In the latter

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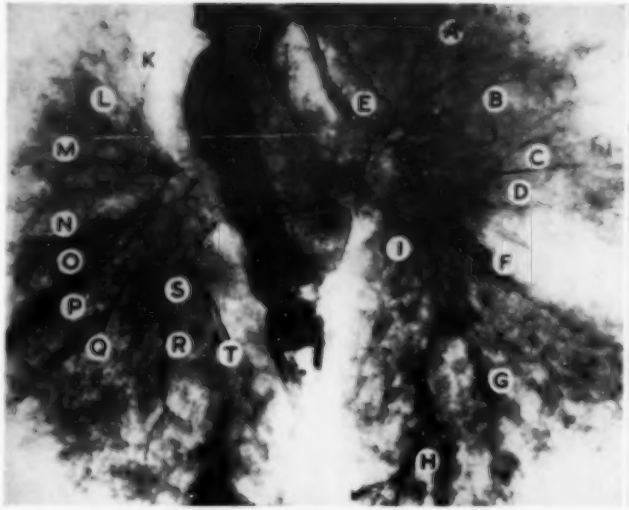


FIGURE 1

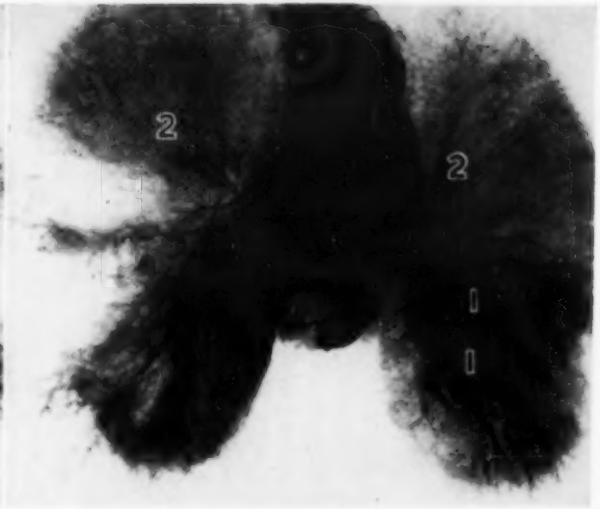


FIGURE 2

Figure 1: Antero-posterior view of normal lungs with bronchial artery visualization. *Left upper lobe:* A—apical branch; B—anterior branch; C—superior lingular branch; D—inferior lingular branch; E—posterior branch. *Left lower lobe:* F—lateral branch; G—anterior branch; H—posterior branch; I—apical branch. *Right upper lobe:* K—pleural branch; L—apical branch; M—anterior branch. (Posterior branch not well seen in this preparation.) *Right middle lobe:* N—lateral branch; O—medial branch; P—interlobar branch (pleural). *Right lower lobe:* Q—lateral branch; R—anterior branch; S—cardiac (medial) branch; T—posterior branch. (Apical branch not well seen in this preparation.) From Cudkowicz and Armstrong: Thorax, December 1951, vol. 6, p. 350.—*Figure 2:* Emphysematous lungs with abnormal bronchial artery visualization. The aberrant course of the bronchial arteries in the left lower lobe is shown: 1—anastomoses with the peripheral branches of the pulmonary arteries; 2—constricted bronchial arteries to both upper lobes. From Cudkowicz and Armstrong: Thorax, March 1953, vol. 8, p. 53.

there is a shift of the mediastinum to the opposite side, similar to the effects of a tension pneumothorax, while in the former there is no mediastinal shift.

It is well known that the lungs have a dual blood supply. The pulmonary arteries have been studied extensively and their function clarified to a large degree, but there is still a great deal of controversy as to the true nature and function of the bronchial arterial system. Bronchial arteries have a multiple origin from the aorta and intercostal vessels and immediately form an annulus in the hilar roots with an interlacing that would be difficult to obliterate by external damage or emboli.[12] The bronchial arteries parallel the bronchi, an artery lying on each side of the bronchus with interlacing communications between them. Because of this anastomotic characteristic of the bronchial arterial system it has been difficult to study experimentally the effect of its obstruction on the survival of the lung, and thus conflicting theories have arisen as to its function. Also it has been difficult to study the effect of ligation of the bronchial arterial system because of the complicating ingrowth of systemic collateral circulation. Some authors[17,24] feel that the bronchial arterial system is vestigial, having played its most important role in the development of the fetus, thereafter becoming unimportant unless some disease process involves the

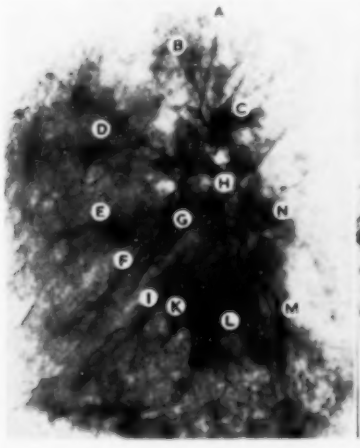


FIGURE 3

FIGURE 4

Figure 3: Lateral view of normal right lung with bronchial artery visualization. *Upper lobe:* A—apical pleural branch; B—apical branch; C—posterior branch; D—anterior branch. *Middle lobe:* E—lateral branch; F—medial branch; G—interlobar pleural branch; H—annulus. *Lower lobe:* I—anterior branch; K—cardiac (medial) branch; L—lateral branch; M—posterior branch; N—apical branch. From Cudkowicz and Armstrong: Thorax, December 1951, vol. 6, p. 351.—*Figure 4:* Lateral view of emphysematous left lung with abnormal bronchial artery visualization. The bronchial arteries fail to reach the areas of emphysema at the periphery and their caliber is very constricted. One-fifth normal size: 1—hilar lymph nodes; 2—no proper annulus formation; 3—absent apical pleural branch; 4—"pigtailing" of bronchial artery to apico-posterior bronchus; 5—bullae. From Cudkowicz and Armstrong: Thorax, March 1953, vol. 8, p. 51.

pulmonary arterial system. Others,[3-6,10,15,16,21,22,26,30,31,33] including the author, believe that the bronchial arteries play a much more important role, namely that of nourishing the lung. It is felt that they form a valuable nutrient blood supply not only to the lung parenchyma and bronchial tree but also to the vasa vasorum of the pulmonary vessels. It is felt that the pulmonary arterial system may likewise nourish the lung parenchyma in the alveolar regions. However, it is a known clinical fact that the pulmonary artery may be ligated and severed without structural damage to the lung.

If the bronchial arterial system plays the above role and is subjected to the same vascular spastic and endarteritic diseases that occur in the systemic blood vessels elsewhere in the body, a concept tenable since its embryologic origin and structural nature are the same as other systemic visceral arteries, then one may well understand why the lung may lose its elastic properties in the presence of arteriosclerotic and endarteritic changes, as is observed in diffuse hypertrophic emphysema. Extensive vascular damage in the larger bronchial vessels as well as degenerative disease in the pulmonary arteries result in actual destruction of the lung architecture with its replacement by inelastic fibrous tissue ("cotton-candy lung").

Bronchiolar obstruction caused by infection or asthma may be a complicating factor in the disabling nature of degenerative lung disease but it is not an etiological factor in its production. In our series of 50 surgically treated patients, 40 failed to give a history of any episodes that could be clinically interpreted as bronchospastic. Pulmonary artery disease of an obstructive or spastic nature, with resultant pulmonary hypertension, may also be classified as a complication and not as a direct etiological

FIGURE 5

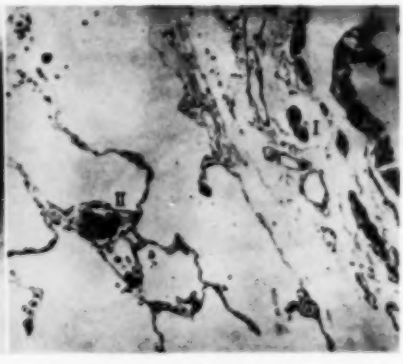


FIGURE 6

Figure 5: Bronchial artery visualization in far advanced emphysema. The aorta and the bronchial arteries can be seen. The bronchial arteries (A) fail to penetrate beyond the hila. The appearance of "pigtailing" is well marked. No extension of the bronchial arteries into the lungs beyond the hila took place. From Cudkowicz and Armstrong: Thorax, March 1953, vol. 8, p. 51.—*Figure 6:* Bronchial arteriole (I) near bronchiolus and (II) in supporting tissue of alveolar wall. (X 175). From Cudkowicz and Armstrong: Thorax, December 1951, vol. 6, p. 355.

factor. Pulmonary artery disease has been found to arise in teen age patients and is present to some degree in all middle aged adults. A combined obliterative change in both artery systems, developing independently or relatedly, may well be the cause of "cotton-candy lung".

The increase of residual air in degenerative lung disease is due to loss of elastic recoil and not to the trapping of air due to bronchospasm. This has been verified by McIlroy and Christie.[25] Clinically this increase of residual air is manifested by the hyperinflated chest. This accounts for the poor respiratory exchange and ineffective cough.

The patient with uncomplicated degenerative lung disease presents a typical clinical picture. His only complaint at first is unaccountable dyspnea on exertion, but later this dyspnea may be present at rest. Finally, orthopnea and cyanosis develop. Eventually these patients may die of cor pulmonale or cardiorespiratory failure if the destructive cycle is not interrupted. Symptoms are greatly aggravated by smoking, asthma, or respiratory infections which always run a prolonged course in such cases.

Physical examination usually reveals a thin anxious patient, using only his accessory muscles for respiration. In advanced stages of the disease, the patient assumes a characteristic sitting position, leaning forward so that his arms rest on his knees in order to support his shoulder girdle during respiration. Breath sounds are markedly depressed throughout the lungs. The antero-posterior diameter of the chest is greatly increased, while the transverse diameter remains constant. Often there is little motion

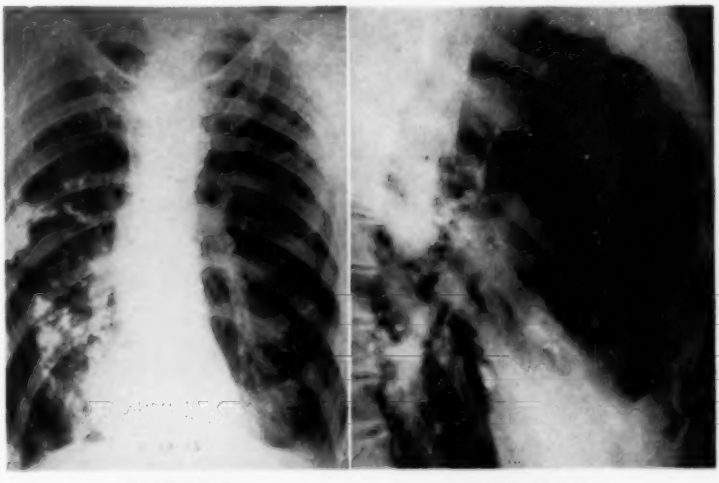


FIGURE 7 FIGURE 8

Figures 7 and 8: Postero-anterior and lateral roentgenograms of far advanced degenerative lung disease, showing residual lipiodol and extensive degeneration throughout both lung fields. The lateral view reveals marked increase in the postero-anterior diameter. This patient gave no clinical history of bronchospasm, merely progressive dyspnea. Three weeks after a right upper lobe resection, death occurred due to failure of healing in the bronchial stump.

of the rib cage other than its actual lifting by the accessory muscles of respiration.

Routine laboratory work generally shows a high erythrocyte count and a high hemoglobin.

Roentgenograms reveal an increased antero-posterior diameter of the chest with a radiolucency of the lung fields in the upper lobes or basal areas. These radiolucent areas in the upper lobes frequently displace downward the visible vascular pattern. Lipiodol bronchograms show a similar downward displacement of the bronchi, and non-filling of the radiolucent areas. The diaphragms are flattened. The cardiac silhouette is asthenic. The mediastinum is in the midline, in contradistinction to the shift of the mediastinum in tension pneumatocele or pneumothorax. It is of interest that the radiolucent areas have a loose fibrous stroma and do not produce compression of surrounding pulmonary parenchyma. Diagnostic bronchoscopy is of no value.

Pulmonary ventilation studies show reduced inspiratory reserve capacity, markedly reduced maximum breathing capacity, and increased residual air.

Extensive dry bronchiectasis with bronchiolar obliteration but without bronchial obstruction or pneumonitis, where the alveoli or air spaces are filled by air-drifts from neighboring normal segments,[9] may offer an extremely difficult differential clinical diagnostic problem. Such patients often present symptoms of ineffective cough and progressive dyspnea, and their roentgenograms show increase in the antero-posterior diameter of the chest. However, bronchiectasis can be definitely diagnosed by a history of recurrent bronchial infections and bronchograms. In bronchiectasis there is an increase in the bronchial artery vascularization while in degenerative lung disease there is a decrease.

FIGURE 9

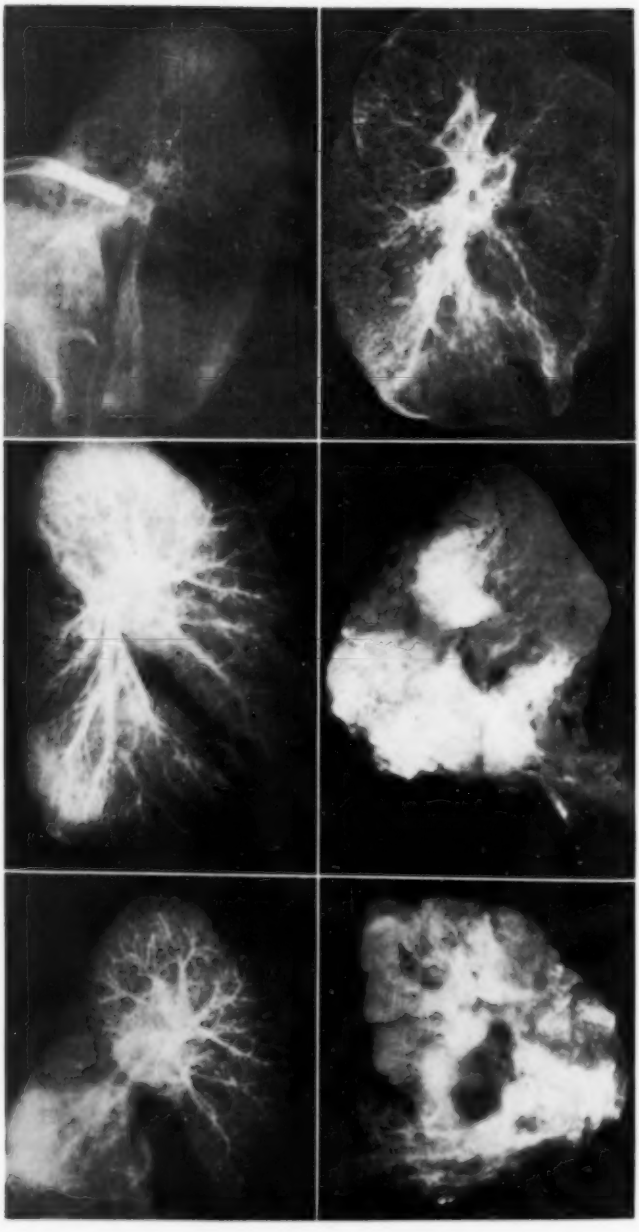
FIGURE 10

Figures 9 and 10: Postero-anterior and lateral bronchograms of extensive degenerative lung disease, in which the middle and lower lobes on the right have vanished. Note there is no shift of the mediastinum nor evidence of compression of remaining lung.

Pathology

Gross pathology: Grossly there is loss of elasticity of the parenchyma, avascularity, and increased fibrosis. There is structural change with complete loss of normal architecture, often extending back to the hilar roots, and replacement by inelastic air-filled sacs having interlacing fibrous stroma. Both pulmonary and bronchial vessels show obliterative changes, and in advanced cases they may vanish altogether. Bronchi show dissolution, absence of obstruction and they terminate in air-filled sacs. The pleura becomes fibrosed, appearing not unlike parchment. The destroyed lung is usually clearly demarcated from surrounding hypertrophic emphysema. In diffuse hypertrophic emphysema the work of Cudkowicz and Armstrong[12-14] shows that, in some cases, bronchial artery occlusion may occur at or proximal to the annulus. Their bronchial vascular injection studies show changes varying from reduction in caliber to total absence of the bronchial vessels. In tuberculosis where destruction of the pulmonary arterial system by endarteritic changes and bullous emphysema are present

FIGURE 11: From case shown in Figures 7 and 8. A cross section of left lung, which appeared comparatively normal on the x-ray film. This photographic cross section shows widespread degeneration and bullous formation in the lung parenchyma.



the bronchial arteries fail to reach these areas. "Vanishing" or "cotton-candy" lung develops due to slowly progressive obliterative changes in the bronchial and pulmonary arterial systems.

Microscopic pathology: In diffuse hypertrophic emphysema, microscopic sections show loss of alveoli and their capillary bed with rupture of alveolar septa, forming irregular air spaces without compression. Throughout the section there is a partial loss or absence of elastic tissue. Patchy endarteritic changes in arterioles are seen. Commonly these changes include medial thickening with hyalinization and intimal thickening producing a small vascular lumen.

In bullous disease and "cotton-candy" or "vanishing" lung disease there are large irregular air-filled spaces with a scattered fibrous stroma and no visible elastic fibers. There is an occasional blood vessel with its own supporting elastic wall. Normal alveolar architecture is completely lost.

Liebow et al.[23] have demonstrated the presence of microscopic vascular shunts in emphysema. Cudkowicz and Armstrong[12] have demonstrated a normal bronchial pattern, showing the presence of bronchial arteries as far as the septa with distribution equal among all segments. In emphysema they demonstrated obliterative changes near the hilus with diminution or absence of vessels in the areas of advanced disease. They[14] also proposed the theory that the bronchial artery to pulmonary artery shunts may be harmful in a two-fold manner: (1) blood flow from high pressure to low pressure systems increases the right heart load, contributing to cor pulmonale; and (2) the nutrient blood destined for the pulmonary parenchyma is partially shunted away from it.

Treatment

The medical regimen, depending upon the extent of the disease, includes the use of expectorants to improve bronchial drainage, complete abstinence from smoking, the judicious use of antibiotics, intermittent positive pressure breathing, and efforts to elevate and improve the function of the diaphragm by belts, pneumoperitoneum, as well as education of the patient in abdominal breathing. At times bronchodilators and mucosal shrinkage drugs are helpful. In the presence of cor pulmonale a salt-free diet and diuretics are indicated. The medical regimen gives only symptomatic relief by increasing the ventilatory powers and aiding in the maintenance of an open air-way. Frequently it is used in preparing the patient for surgery.

Surgical management, as previously described,[11] consists of resection of air-robbing dead space (bullae and "cotton-candy lung"), denervation of

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Figure 12 (upper left): Roentgenogram of air inflated normal left lung.—*Figure 13 (upper right):* Roentgenogram of air inflated degenerated left lung of patient whose roentgenograms are shown in Figures 7 and 8.—*Figure 14 (left center):* Roentgenogram of injected normal pulmonary artery tree. — *Figure 15 (right center):* Roentgenogram of degenerated right upper lobe in which the pulmonary artery tree has been injected. Note complete absence of pulmonary artery system. (Same case as shown in Figures 7 and 8).—*Figure 16 (lower left):* Roentgenogram of injected normal pulmonary veins.—*Figure 17 (lower right):* Roentgenogram of degenerated right upper lobe in which the pulmonary veins have been injected. Note complete absence of pulmonary veins. (Same case as shown in Figs. 7 and 8).

Figure 18: (A) Microscopic section of pulmonary emphysematous lung showing loss of alveoli and chronic bronchitis with peribronchial inflammatory changes. An associated artery is shown at the top. (X 100).—(B) Enlargement of the artery seen in (A), showing advanced medial and intimal thickening. (X 400). From Crenshaw and Rowles: J. Thoracic Surg., October 1952, vol. 24, p. 401.

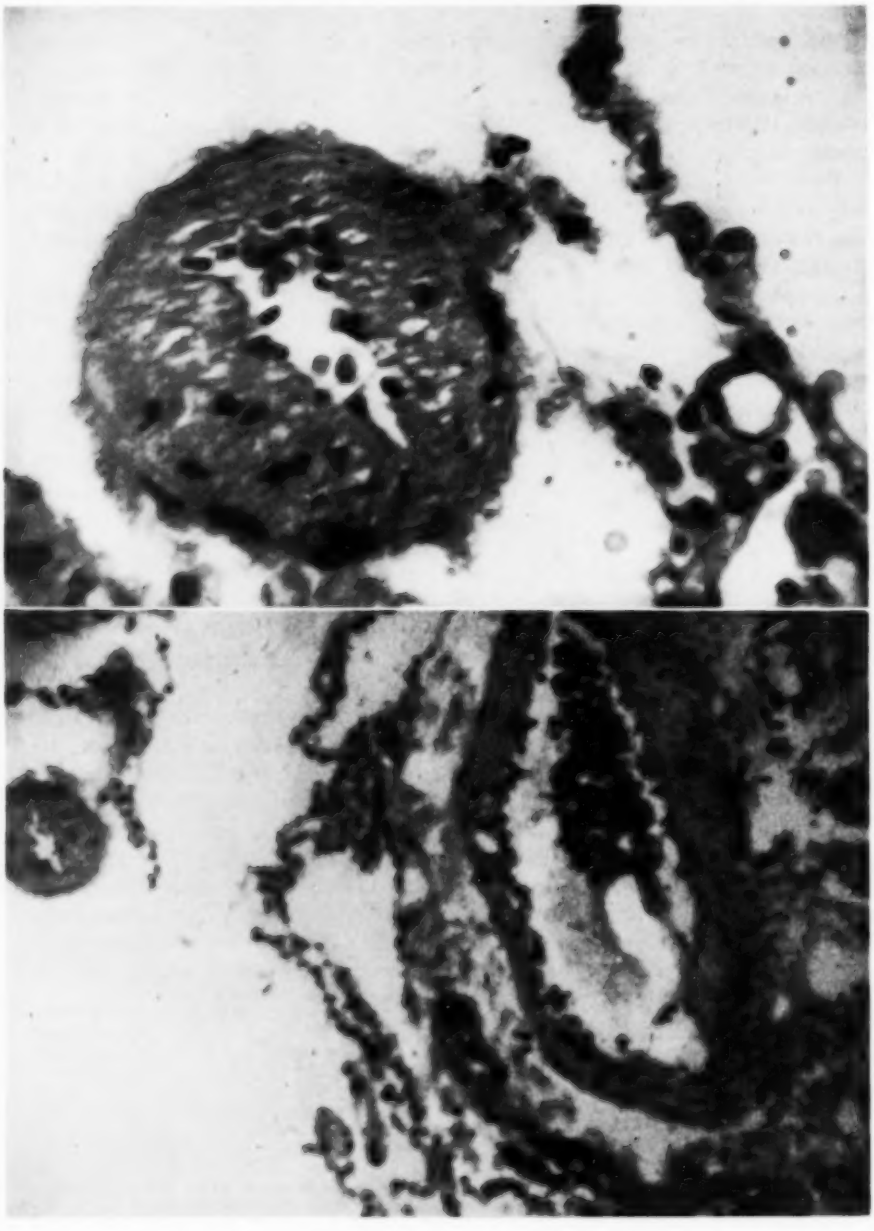

FIGURE 18B

FIGURE 18A

the lung by severing the vagus and sympathetic chains, and visceral chest wall symphysis (parietal pleurectomy and poudrage) in an effort to encourage collateral systemic nutrient circulation from extrapulmonary sources.

Resection of degenerated areas makes more air available for the functioning lung in these respiratory cripples. These degenerated areas are air-robbing, not air-trapping. Because of the ease of air-flow into and out of dead space, air flows more easily into the inelastic degenerated areas, thus reducing the volume of air entering the normal lung tissue where it must overcome the resistance of the natural elastic recoil. Surgical treatment may require segmental or lobar resection, or clamp resection of smaller degenerated areas.

Complete vagal denervation is accomplished by severance of branches at the hilum, including those from the left recurrent laryngeal nerve. Experimental work in dogs[20] has shown that, in the presence of artificially produced pulmonary hypertension, when all branches of the vagus to the lung are severed there is a lowering of this hypertension, thus reducing the burden on the right ventricle. The sympathetic chain is extirpated from the third through the ninth ganglia, including the splanchnic nerves. Since the bronchial vessels are anatomically systemic blood vessels it is thought that sympathectomy has the same effect here as it has in other parts of the body.

Visceral chest wall symphysis is enhanced by removing the parietal pleural barrier from the pleural space. Sterile talc poudrage is done[12] to produce a nonconstrictive irritation to augment the ingrowth of systemic collateral circulation.

Discussion

It would seem from the facts presented in this paper that hypertrophic emphysema, in its various stages, is a degenerative vascular disease involving first the bronchial and, secondarily, the pulmonary artery system. These changes begin in the periphery of the lung and, depending upon the extent and location of vascular damage, cause localized or diffuse lung destruction.

In the author's concept, bronchospasm, bronchial infection, and cardiac failure are separate entities complicating the primary obliterative endarteritis. This is supported by the fact that in our series of patients, in the advanced stages in which they are now being seen, approximately 75 per cent give no history of bronchospasm. Other investigators[8] have attempted unsuccessfully to relieve the bronchospastic feature of asthma by denervation of the lung. In considering this same bronchospastic element as an etiological factor in the production of diffuse hypertrophic emphysema, they have similarly attempted to alleviate this element of bronchospasm in the latter disability,[1,2] and have attained clinical improvement. In the author's experience, where bronchospasm has been a complicating factor in emphysema, such patients have been benefited by complete denervation. We believe this benefit is due, however, to the changes produced in the

two vascular systems in the lung rather than to any effect upon bronchospasm. In emphysema vascular studies of both systems reveal gross changes and in "vanishing" or "cotton-candy" lung the vessels are obliterated near the hilum. It is not conceivable that such obliteration could be caused by bronchospasm. When these patients have asthmatic attacks they have them as severely on the denervated side as on the opposite unoperated side. The reason for the benefit received, as expressed by the work of Kaunitz,[20] is due to a lowering of the pressure in the pulmonary vascular system with its reduction in the work load of the right heart, as well as a sympathectomy effect upon the systemic bronchial arterial circulation.

One of the reasons it has been difficult to study the effect of ligation of the bronchial arterial system is because of the rapid ingrowth of collateral circulation from the mediastinal and chest wall systemic vessels.[12-14] This has a clinical application, as reported by Barrett and Daley,[7] where, in the presence of complete pulmonary stenosis, life has been maintained by the surgical induction of systemic collateral circulation to the lung. We feel that surgically induced systemic collateral circulation is likewise applicable in emphysema by preventing or correcting reversible structural changes resulting from obliteration of the bronchial and pulmonary arterial systems.

It is not possible to surgically remove all of the destroyed lung, nor is one able to estimate how much of the badly crippled lung can be returned to partial or complete function. However, the medical treatment available at the present time furnishes only temporary and symptomatic relief to the patient and does not correct the underlying obliterative or spastic vascular disease. The medical program, in the main, attempts to improve the airway and the mechanics of respiration, and to control infection. The effects of so-called bronchodilator drugs may be due as much to their shrinking effect on the bronchial mucous membranes as to relief of bronchospasm.

In grossly destroyed degenerated lungs, which in our patients have occurred in heavy smokers, the gross pathology can be likened to a pulmonary Buerger's disease. We have also seen three cases of primary bronchogenic carcinoma arising in degenerated lung areas.

In our series of 50 cases we have had three deaths occurring within a period of three weeks following surgery. One death was due to persistent air leakage, another to bronchopleural fistula, and the third to cardiorespiratory insufficiency. There had not been sufficient time to allow for ingrowth of systemic collateral circulation. However, two deaths have been reported[29] from gastric carcinoma eight months after surgery performed for degenerative lung disease. Autopsy findings in these two cases revealed widespread ingrowth of systemic collateral vessels between the chest wall and the remaining lung.

All of the other 47 patients in our series have shown clinical improvement. Even the patients with extreme respiratory crippling tolerated surgery surprisingly well although in some the postoperative course was stormy.

Improvement has ranged from a return to limited activity to a return to full-time work.

The results of surgery are dependent upon the extent of pulmonary destruction. There has been an immediate improvement, even during surgery, due to the removal of air-robbing dead space which allows expansion and aeration of the normal lung. It has also been frequently noted during operation that there is a marked change in the color of the blood, showing improved oxygenation. However, the continued improvement in these patients must be attributed to the gradual ingrowth of systemic collateral circulation. It is well understood that these surgical procedures cannot prevent further arteriosclerotic changes, but the ingrowth of new nutrient vessels protects the lung against further destruction.

SUMMARY

1) Degenerative lung disease includes diffuse hypertrophic emphysema, bullous emphysema, and "vanishing" or "cotton-candy" lung. These clinical entities are various stages of one disease process having a common pathological factor, namely obliterative vascular disease of both the bronchial and pulmonary arterial systems.

2) Patients with degenerative lung disease present a typical clinical picture of progressive dyspnea, restricted respiratory movement, and suppressed breath sounds. Their roentgenograms reveal an increased anteroposterior diameter, and, frequently, radiolucent areas in the apices or bases. The mediastinum is in the midline in contradistinction to the mediastinal shift in tension pneumatocele or spontaneous pneumothorax.

3) Bronchospasm, bronchiolar obstruction, and cor pulmonale are complications rather than etiological factors in degenerative lung disease.

4) Smoking may be etiologically significant in the development of obliterative vascular changes similar to those occurring in Buerger's disease. All of the patients with "vanishing lung" disease in our series were heavy smokers.

5) Medical management to date has given only temporary symptomatic relief and has not corrected the pulmonary degenerative cycle. Surgical management aims at improving ventilation, lowering pulmonary hypertension, increasing alveolar vascular channels, and promoting systemic collateral circulation.

6) Segmental or lobar resection of "stretched cysts" means removal of air-robbing dead space, and allows more air to become available to the remaining normal lung in these patients with limited expiratory excursions.

7) Clinical results in surgically treated patients depend upon the amount of lung destruction that has taken place. These results range from slight to dramatic improvement.

8) The purpose of this paper is to encourage greater interest in this deserving group of patients and possibly to shift the emphasis of therapy from the palliative regimen of maintenance of an adequate airway and increasing ventilatory properties, to a direct surgical attack upon the irreversible cause of this disabling disease, namely endarteritic obliterative vascular disease.

RESUMEN

1) El enfisema pulmonar degenerativo crónico difuso e hipertrófico, enfisema buloso y el "pulmón evanescente" o "pulmón en dulce de algodón". Todas estas entidades patológicas son etapas varias de un proceso patológico que tiene un factor etiológico común: la enfermedad vascular obliterante tanto del árbol bronquial como del arterial pulmonar.

2) Los enfermos con enfermedad degenerativa del pulmón, presentan un cuadro clínico de disnea progresiva, disminución de los movimientos respiratorios y supresión del murmullo respiratorio. A los rayos X se observa un aumento del diámetro anteroposterior y frecuentemente áreas translúcidas en los vértices o en las bases. El mediastino está en la línea media por el contrario de lo que sucede en el neumatocele a tensión o en el neumotórax espontáneo.

3) El broncoespasmo, la obstrucción bronquiolar y el cor pulmonale son complicaciones más bien que factores etiológicos en la enfermedad degenerativa pulmonar.

4) El fumar puede tener significación etiológica en el desarrollo de los cambios vasculares obliterantes similarmente a lo que ocurre en la enfermedad de Buerger. Todos los enfermos de nuestras series con "pulmón evanescente" eran grandes fumadores.

5) El tratamiento médico hasta la fecha ha dado solo mejoría temporal y no ha corregido el ciclo pulmonar degenerativo. El tratamiento quirúrgico intenta mejorar la ventilación, disminuir la hipertensión pulmonar, aumentar los conductos vasculares alveolares, y provocar la circulación general colateral.

6) La resección segmentaria o lobar de "bolsas distendidas," significa la supresión de espacio muerto que "roba" aire y permite que más aire sea aprovechable por el resto del pulmón normal en enfermos con limitadas excursiones respiratorias.

7) El resultado clínico en enfermos tratados quirúrgicamente depende de la cantidad de pulmón destruido. Estos resultados varían desde la mejoría ligera traumática hasta el más sorprendente mejoramiento.

8) El propósito de este trabajo, es alentar el mayor interés por estos enfermos que lo merecen y posiblemente el desviar el énfasis sobre el tratamiento, del régimen paliativo de mantenimiento paso de aire adecuado hacia el ataque quirúrgico directo sobre la causa irreversible de esta enfermedad incapacitante que es la endarteritis obliterante.

RESUME

1) La maladie dégénérative du poumon, l'emphysème hypertrophique diffus, l'emphysème bulleux, réalisent différents stades d'un seul processus dont l'étiologie est commune, c'est-à-dire l'oblitération basculaire d'artères bronchiques et pulmonaires.

2) Les malades atteints de maladie dégénérative du poumon présentent un tableau clinique caractéristique de dyspnée progressive, de diminution des mouvements respiratoires, et de suppression du murmure vésiculaire. Leurs radiographies montrent l'accroissement du diamètre antéro-pos-

térieur, et fréquemment des zones d'hyperclarté aux sommets et aux bases. Le médiastin reste à la partie médiane contrairement à ce qui se passe dans les kystes "ballons" ou dans les pneumothorax spontanés.

3) Le bronchos-spasme, l'obstruction bronchiolaire et le coeur pulmonaire sont beaucoup plus des complications que des facteurs étiologiques de la maladie dégénérative du poumon.

4) Le tabac peut être un facteur étiologique valable pour l'oblitération des vaisseaux par analogie avec ce qui se passe dans la maladie de Buerger. Tous les malades atteints de poumon bulleux parmi ceux qu'a vus l'auteur étaient de grands fumeurs.

5) Les traitements médicaux utilisés jusqu'à présent n'ont donné que quelques améliorations symptomatiques, et n'ont pas empêché l'évolution de la dégénérescence pulmonaire. Les traitement chirurgicaux ont pour objet de favoriser la ventilation, alleger l'hypertension pulmonaire, augmenter le calibre des canaux alvéolaires, et favoriser la circulation collatérale.

6) L'exérèse segmentaire ou lobaire dans les cas de kystes étendus permet la suppression d'un espace mort, et permet qu'une quantité plus importante d'air puisse être utilisée par le poumon normal restant chez ce malade, dont la course respiratoire est limitée.

7) Les résultats cliniques chez les malades traités chirurgicalement, dépend de l'importance de la destruction pulmonaire. On peut les voir évoluer depuis des améliorations légères jusqu'à des améliorations spectaculaires.

8) Le but de cette communication est d'augmenter l'intérêt que l'on porte à ce type de malades; il faudrait également transformer la thérapeutique uniquement palliative, et ayant pour but de maintenir une oxygénation suffisante et d'augmenter les possibilités ventilatoires en une attaque chirurgicale directe portant sur la cause irréversible de la maladie, c'est-à-dire l'atteinte vasculaire, l'oblitération endartérielle.

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Experiences with Retroclavian Lymph Node Biopsy in the Diagnosis of Certain Intrathoracic Diseases*

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The accurate diagnosis of intrathoracic diseases is sometimes difficult. When ordinary routine examination methods fail, differentiation often requires biopsy of enlarged superficial lymph nodes. For cases in which no such nodes can be found Daniels (1949) recommended the histological examination of lymph nodes from the mass of fatty tissue between the M. sternocleidomastoideus and the M. scalenus anterior. These nodes forming part of the mediastinal lymphatic system. He reported five cases: a diagnosis of Boecks sarcoid was established in two, carcinoma in two and silicosis in one. He points out that in one with cancer a major operation was prevented and that, in the other a major exploration of the lung would not have been necessary if biopsy had been carried out first.

In 1951 Weiss and alii reported a case of pulmonary sarcoidosis in which a clinical impression of sarcoidosis was confirmed by the method of Daniels.

Stimulated by these reports which seem not to have been duly appreciated, and convinced that the chance of getting informative material would be great even in cases in which no lymph nodes could be felt when the subclavicular region was exposed and the above mentioned fat pad explored, we have tried this procedure since January 1952 in a series of 56 cases. In all of them the clinical and/or roentgenological pictures suggested pulmonary or mediastinal disease but the diagnosis was not established with certainty. In none of them could enlarged lymph nodes be found, despite careful palpation.

Sometimes preoperative palpation gave the impression of an enlarged lymph node in the supraclavicular space close to the lateral border of the sternocleidomastoideus muscle, but exploration showed the supposed node to be the lateral part of the omohyoideus muscle.

The surgical technique is simple and the procedure takes only 10 to 15 minutes. In local anaesthesia an incision of 3 to 4 cm. is made on the side of the lesion or, if both sides are equally involved, the right side about two fingerbreads over and paralleling the clavicle through the skin and the platysma. The lateral border of the sternocleidomastoideus muscle may be devided. This muscle is retracted medially and the fat pad on the anterior surface of the scalenus anterior muscle thereby exposed. This space is crossed by the inferior thyroid and transverse cervical vessels and is bordered by the subclavian and internal jugular veins, the omohyoid and scalenus anterior muscles. The phrenic nerve and—on the left side—the thoracic duct—on the right side—the right lymphatic duct are to be considered. Care should be taken to avoid injuring these structures. This

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fat pad contains lymphoid tissue which is part of the mediastinal lymph system. There may be visible or palpable lymph nodes to exstirpate. If not, the pad is removed totally or subtotally for microscopical examination. The incision is closed. The patient's discomfort during and after the operation is slight. Healing was complicated in one case by the occurrence of a slight haematoma and in another by a couple of weeks' discharge of a chylus-like fluid, despite the fact that the operation was done on the right side. The technique is simple; however, the operation should be performed by an experienced surgeon because of the important anatomical structures in or around the operation field. In some cases we have left silver clips in the lowest part of the intrathoracic wound to show how far the resection had been carried down the mediastinum (Figure 1).

Altogether 56 patients were submitted to such bloc dissections. Chest radiographs that had led to systematical examination were taken 32 times as a routine procedure or during mass x-ray of the population and 24 times because of different symptoms as shown in Table I. In 42 cases there were hilar lymphomas, associated in 18 cases with lung findings. Lung changes without any marked hilar enlargement were present 11 times. In one case there was a mediastinal tumor and in two pleurisy of unknown origin (Table II). The biopsy of the fat pad showed lymph nodes or lymphoid tissue in all cases, with a microscopical diagnosis of sarcoidosis or epitheloid cell granulomatosis in 31, of tuberculosis in one, of mononucleosis

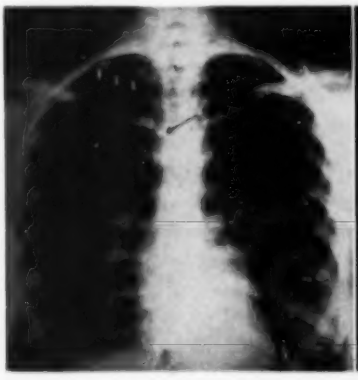

FIGURE 1

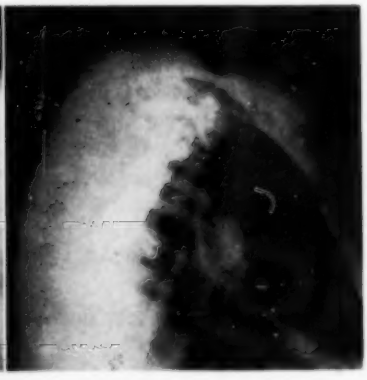

FIGURE 2

TABLE I

Chest X-ray Made Because:	
Routine or mass examination	32
Erythema nodos. and/or joint pains	11
Dermatitis	2
Iridocyklit	2
Cough and/or fever	9
TOTAL	56

in one, of non specific inflammatory changes in 17, and of normal lymph tissue in six. The method thus gave a positive aid to the definite diagnosis in 60 per cent of these cases. The roentgenographical and the histological findings as shown in Table II.

In three cases the clinical diagnosis was quite obscure. The biopsy did not unveil two but contributed to the diagnosis in the third case. Of 45 patients with clinical symptoms characteristic or suggestive of sarcoidosis biopsy proved the diagnosis in 30 (66 per cent). The information the method gave in eight cases with clinical symptoms of disease other than sarcoidosis is also summarized in Table III.

In 1952 Lofgren and Lundback published a study of the relation of the bilateral hilar syndroma to tuberculosis and sarcoidosis founded on 212 cases. They stress the importance of careful palpation of the supraclavicular fossa, the anterior, median portion close to the attachment of the sternocleidomastoideus muscle being the typical site of enlarged lymph nodes, more often to the right than to the left. Earlier when palpation was

TABLE II

RELATION BETWEEN X-RAY AND BIOPSY FINDINGS

		BIOPSY FINDINGS					
Chest X-ray Findings	No.	Sarcoidosis	Epiteloidcell Granulomatos	Tuberc.	Unspec. Infl.	Mononucl.	Normal
Bilat. hilar lymphoma (B.H.L.)	24	13	3		6		2
B.H.L. Plus lung findings	18	10	1		7		
Lung findings	11	3	1	1	3		3
Mediast. tumor	1						1
Pleurisy	2				1	1	
TOTAL	56	26	5	1	17	1	6

TABLE III

CLINICAL DIAGNOSIS

		With Aid of Histopatological Examination				Histopat. ex. of no Aid to Clinical Diagnosis
	No.	Sarcoidosis	Tuberc.	Mononucl.	Septic Pancardit.	
Sarcoidosis or sarcoidosis?	45	30				15
Tuberculosis	5	1	2	1		1
Tuberc. or tumor	1		1			
Mediast. tumor	1					1
Reticulosis?	1					1
Open	3				1	2
TOTAL	56	31	3	1	1	20

done less systematically lymph nodes were found only in about 9 per cent of the cases examined as compared with 47 per cent during the last half year of their investigation. Such (palpable) nodes were removed in 55 cases, 43 of them showing sarcoidosis, one tuberculosis and 11 sinus catarrh. In some cases sarcoidosis was found in one lymph node and non-specific sinus catarrh in an adjacent.

Our investigation seems to indicate that the subclavian biopsy is another step further towards accurate diagnosis.

We have found the results of the subclavian bloc dissection far superior to tonsillectomy which was recommended by Schaumann in sarcoidosis and at the same time less trying for the patient. The other methods to obtain material for biopsy such as excision of muscular tissue or bone marrow seem not to have given satisfactory results.

Subclavian bloc dissection with histological examination of the lymph nodes seems to be a valuable method in the diagnosis of obscure intrathoracic disease especially in those cases in which no superficial enlarged lymph nodes are felt and the x-ray investigation or the clinical picture suggests sarcoidosis.

SUMMARY

Bloc dissection of the fat pad between the sternocleido-mastoideus and the anterior scalenus muscles has been performed in 56 cases with x-ray shadows of different intrathoracic diseases. Histo-pathological examination showed typical sarcoidosis in 26 cases and sarcoidosis was suspected in five. Tuberculosis was found in one and nononucleosis in one. In 17, there were non-specific inflammatory changes and in six normal lymph tissue.

Out of 45 typical or strongly suspected cases of sarcoidosis without palpable lymph nodes the diagnosis was confirmed in 30 (66 per cent). The method published by Daniels in 1949 seems not to have been duly appreciated.

We recommend the method as a simple way to get material for histological examination in cases of intrathoracic diseases of doubtful etiology without palpable enlarged lymph nodes.

RESUMEN

La disección en bloque de la grasa del paquete entre el esterno mastoideo y el escaleno anterior, se ha llevado a cabo en 56 casos con aspectos radiográficos de sombras de diferentes enfermedades intratorácicas. El examen histopatológico mostró sarcoidosis típica en 26 casos y se sospechó sarcoidosis en otros cinco.

La tuberculosis, se encontró en uno y mononucleosis en uno. En 17, no hubo cambios inflamatorios y en seis, se encontró tejido linfático normal.

De 45 casos típicos o fuertemente sospechosos de sarcoidosis, sin ganglios palpables el diagnóstico, se confirmó en 30 (66 por ciento). El método publicado por Daniels en 1949, parece no haber sido apreciado debidamente.

Recomendamos el método como una manera sencilla de obtener material

histológico para examen en casos de enfermedades intratorácicas de etiologia dudosa sin ganglios palpables.

RESUME

Les auteurs ont pratiqué la dissection en bloc de la couche graisseuse qui s'étend entre le sterno-cléido-mastoïdien, et le muscle scalène. Cet examen à été pratiqué dans 56 cas pour lesquels l'exploration radiologique avait révélé différentes affections intra-thoraciques. L'examen histologique à montré une maladie de Besnier-Boeck-Schaumann typique, 26 fois, et à permis de suspecter cette affection dans cinq cas. Dans un cas, il s'agissait de tuberculose, dans un autre cas de mononucléose infectieuse. Chez 17 malades, il y avait des altérations inflammatoires sans caractère spécifique, et chez six, le tissu lymphatique était normal.

Parmi les 45 cas où la maladie de Besnier-Boeck-Schaumann fut observée, où suspectée sans qu'il y ait eu de ganglions palpables, chez trente malades, le diagnostic se trouva confirmé (66%). Il semble que la méthode publiée par Daniels en 1949 n'ait pas été appréciée à sa juste valeur.

Les auteurs recommandent la méthode comme un moyen simple d'obtenir la possibilité de pratiquer l'examen histologique dans des cas d'affection intra-thoracique dont l'étiologie est douteuse et qui ne s'accompagnent pas d'adénopathies palpables.

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Intrafamilial Contagion in Chronic Sino-Respiratory Infections*

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The problem of chronic sino-respiratory infections which includes sinusitis, bronchitis, bronchiectasis and infective asthma is of great magnitude. Although these illnesses do not immediately endanger the life of the patient they seriously affect the health of many individuals. It is estimated that approximately 2,000,000 people in this country suffer from chronic bronchitis and 1,250,000 from sinusitis.[1] With asthma due to infection included, approximately 3,000,000 to 4,000,000 are sufferers of chronic broncho-pulmonary disease. Bronchitis alone is responsible for the largest average absenteeism in industry and exceeds the common cold in terms of time lost from productive work.[2]

For the past eight years the author has concerned himself with the problem of infection in the respiratory tract, in view of the frequency of these infections in allergic patients.[3] At first, attention was paid to the use of antibiotics in combating infection; preferably this was administered in aerosol form to achieve maximum concentration within the respiratory tract, although secondary absorption and systemic action could be demonstrated with penicillin and streptomycin. A method of administering long-lasting aerosols, utilizing open and closed methods of treatment, and a tent and closed chamber (bathroom) for treatments of infants and children, was developed.[4] Subsequently, to achieve more specific therapy with the antibiotics, bacteriologic methods were introduced which included the use of cultures, and the performance of in vitro inhibition tests.[5] This unquestionably improved the results of the treatment. Nevertheless, it soon became apparent that the problem was not the control of specific incidents of infection but *how to prevent the recurrence of infection*, since this seemed to be inevitable in most patients. At times it was noted that despite adequate therapy with specifically-selected antibiotics, cultures taken revealed the presence of the offending organisms in the respiratory tract. This was particularly true for the hemolytic staphylococcus and some strains of streptococci. In others it was noted that these organisms were apparently eliminated as a result of therapy, only to be isolated again with a recurring infection. Then again, when several members of a family were treated simultaneously, and cultures were taken from them, it was frequently noted that there was a commonality of potentially pathogenic organisms. Attention was, therefore, focused on contagion as an important

*This is the 5th of a series on a Bacteriologic and Epedimiologic approach to the Treatment of Sino-respiratory Infections.

The bacteriologic studies were performed by The Biological Laboratories, Brooklyn, New York.

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factor in maintaining chronic sino-respiratory infection within the family group.[5,6] The possible existence of a carrier state within the family, and the search for foci of dissemination of respiratory infection was then pursued, and is the subject of this communication.

Our investigation of the carrier state within the family was first reported in observations which covered 43 persons in 17 family units, from whom cultures were taken 68 times and 159 organisms isolated. The data revealed the possibility of the existence of a family source of contagion in 10 of the 17 families in which only selected members were studied. This preliminary data was subsequently fortified by a more thorough investigation of 28 additional families (comprising 63 individuals) in 17 of which evidence was encountered of contagion and a carrier state.[6] This series was more representative of the family, and consisted of instances in which families of four or five members were investigated regardless of clinical status. In the families studied completely, 11 out of 12 showed evidence strongly suggestive of contagion whereas in the incomplete family group only six out of 10 showed such possible relationship. In some of the families three to four out of five members had identical organisms presumably pathogenic. This not only included a single organism but at times even two or three organisms, with most of the members of the family exhibiting disease-producing organisms, although illness was not apparent, except for the patient. Altogether 39 families were studied, of which 27 showed bacteriologic evidence suggesting the existence of a carrier state. It should be emphasized that not all members of a family were investigated. Were the investigation to have included every member of the family, it would seem that the incidence of a carrier state might have been higher. The data obtained from the observations of these families is recorded in Table I.

The opportunity to study intrafamilial contagion within a large family group, comprising seven family units, was subsequently presented to the author. This occurred during the examination of a dentist, who had been subject at different times to frequent colds, sinusitis, tonsilitis, asthma and infections about the eyes. A review of the family history revealed that his mother had been subject to asthma and bronchitis; that his brothers and sisters were subject periodically to frequent episodes of sino-respiratory disease, and that likewise most of their children were similarly afflicted. It was, therefore, arranged to make a study of the seven brothers and sisters, their spouses and their children. The study, made in December

TABLE I: BACTERIOLOGIC EVIDENCE OF CONTAGION IN FAMILIES WITH SINO-RESPIRATORY INFECTION

Series	No. of Families	Complete	Incomplete	No. of Patients	No. of Cultures	No. of Isolates	Possible Contagion
1) 1949	17	6	11	43	68	159	10
2) 1950	22	12	10	63	73	144	17
TOTAL	39	18	21	106	141	303	27

1951, included a questionaire concerning the frequency of sino-respiratory infections, such as the occurrence of frequent colds (more than two a year), tonsilitis, sinusitis, pneumonia, bronchopneumonia, bronchitis, infective asthma and infections in and about the eye. Simultaneously, pharyngeal cultures were taken from the 25 members of the families who made themselves available at that time for the investigation. The data obtained of the L. family is presented in Charts I and II. Thus, it is noted that 15 members of the family were subject to more than the average of two colds per year; that 13 of them had a history of repeated tonsilities, and that 14 of them had tonsillectomies; seven were subject to bouts of sinusitis;

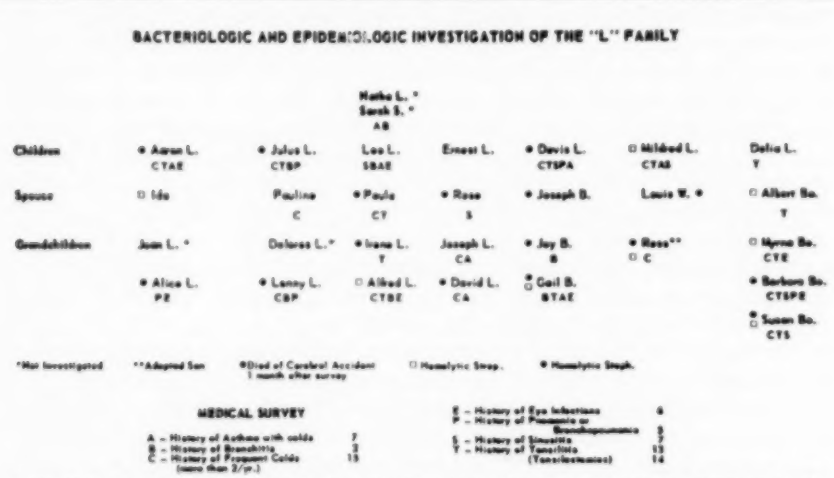

CHART I: Genealogy of the "L" family. The infection is traceable by history to the mother. Five of her children suffered from one or more varieties of sino-respiratory infections. In contrast, their respective spouses were subject to fewer respiratory episodes. Their children, however, continue to show an abnormal incidence of sino-respiratory infections. The frequent occurrence of the hemolytic staphylococcus• indicates these infections to be a familial disease similar to tuberculosis due to contagion within the household

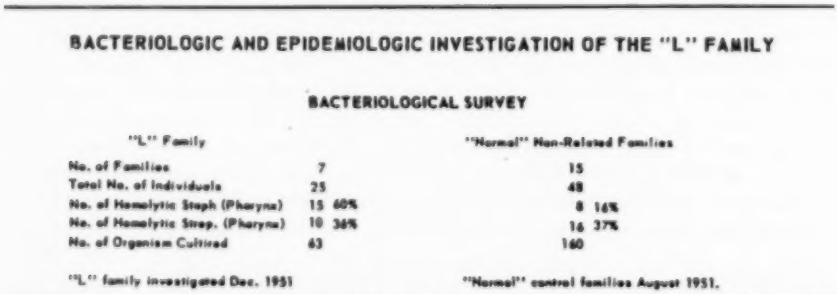
BACTERIOLOGIC AND EPIDEMIOLOGIC INVESTIGATION OF THE "L" FAMILY
BACTERIOLOGICAL SURVEY
"L" Family
"Normal" Non-Related Families
No. of Families 7 15
Total No. of Individuals 25 48
No. of Hemolytic Staph (Pharynx) 15 60% 8 16%
No. of Hemolytic Strep. (Pharynx) 10 36% 16 37%
No. of Organism Cultured 63 160
"L" family investigated Dec. 1951
"Normal" control families August 1951.

CHART II: A comparative bacteriologic study of the seven branches of the "L" family and 15 unrelated "normal" families without history of frequent sino-respiratory and related infections.. The incidence of hemolytic staphylococci in the "L" families as cultured from the pharynx is approximately four times that seen in the "normal" families.

five had pneumonia or broncho pneumonia; two bronchitis; seven asthma associated with infection, and six with infections in and about the eye.

The history of repeated infection implying contagion was confirmed by the bacteriological studies. The hemolytic staphylococcus was cultured from the pharynx in 15 of the 25 individuals studied (an incidence of 60 per cent), and the hemolytic streptococcus occurred nine times (36 per cent). In order to validate these observations as well as the data obtained in the study of the unrelated families, as previously described, a study was undertaken of "normal" families without any history of chronic sino-respiratory infections in any member of the family. This study comprised 15 families, 48 individuals, from whom pharyngeal cultures were taken and 160 isolates obtained. In this group the hemolytic staphylococcus occurred only eight times (an incidence of 16.6 per cent) and the hemolytic streptococcus occurred 16 times (37 per cent), the latter being the same frequency as in the "sick" families. This would indicate that although members of "normal" families tend to harbor proportionately more organisms in their pharynx, these are relatively innocuous, and that the relative percentage of probable pathogens was considerably less in the so-called "normal" group as compared with families in whom there is the presence of chronic sino-respiratory disease. Congnizance is taken of the role of "host resistance" factors when pathogens are present without obvious disease.

In searching further for possible sources of infection or reinfection within the family groups it was noted that there was an unusual occurrence in these people of low-grade infections about the eye such as styes, conjunctivitis and/or blepharitis. A study was, therefore, undertaken of patients suffering from chronic sino-respiratory disease associated with blepharoconjunctivitis and related conditions. This study reported in detail elsewhere, is summarized here.[7] Of 25 patients investigated, ranging in age from one to 63 years, 23 showed concommittant respiratory and eye infections. The remaining two were subject to sino-respiratory disease without infections about the eye; they were, however, intimately exposed to one other member of the family suffering from blepharoconjunctivitis; eight of the 25 individuals displayed blepharoconjunctivitis simultaneously with another member of the family. Six times this involved a mother-patient relationship, since the intimate relationship between mother and child was probably more conducive to the spread of the infection.

The bacteriologic studies which included cultures taken simultaneously from the respiratory tract and from the eye or eyelid, revealed that 13 of 19 patients thus studied showed bacteriologic evidence indicating a commonality of organisms. An analysis of the organisms involved corroborated the findings previously noted within the family groups, in which it was indicated that the hemolytic staphylococcus was encountered in 10 of the 13 individuals in whom there was bacteriologic evidence of relationship between infections in and about the eye and the respiratory tract. This organism was encountered four times more frequently in the "L" families than in the "normal" families. This is not surprising since this organism

is widely distributed, not readily eradicated, frequently develops resistance to antibiotics, and does not readily stimulate sufficient immunity on the part of the host to eliminate it. Therefore, it is apt to produce a chronic infection in either (or both) respiratory and ocular organs.

Although the role of blepharitis and related eye infections has been stressed, it is undoubtedly not the only source of possible reinfection for the respiratory tract. Thus, one patient in addition to the respiratory tract infection, suffered as well from a chronic infection of both ears, and from whom was obtained similar organisms from the ears as well as from the pharynx. In two other patients identical organisms were cultured from chronic skin infections, and from infections in the respiratory tract. It would seem logical, therefore, once one is confronted with the problem of chronic sino-respiratory disease, particularly in children, to look for foci of infection elsewhere in the body (eyes, skin, ears), or from those in intimate contact with the patient, in order to remove sources of contagion.

Discussion

Many observations on the epidemiology of respiratory infections involving wards, nurseries, institutions and barracks, have been reported. This has been due to the fact that frequently the occurrence of respiratory infections in such large groups has been conspicuous and serious; and because of the availability of medical and technical help in these institutions, suitable for detecting carriers within such groups. In sharp contrast there have been no serious studies of the role of the carrier state, and the epidimiological aspects of sino-respiratory infection within the family group. The infections occurring within the family group are usually of the low-grade variety, rarely resulting in fatalities but frequently starting in early infancy when immunity is at its lowest, and burdening the patient with disability for many years, if not an entire lifetime. Nevertheless, this is an important public health problem second only in magnitude to tuberculosis.

Observations on the epidemiology of acute respiratory infections provide useful information as to the possible epidemiology of chronic sino-respiratory infections. Smiley and his collaborators have at verious times reported on the epidemiology of pneumonia. In one instance, a large state hospital for the insane suffered an epidemic of pneumonia following a rather mild outbreak of influenza.[8] More spectacular was the recounting by the same authors of the invasion of a specific pneumococcus (type 14) in a group of normal children in a nursery in which this virulent strain subsequently caused pneumonia in many infants and children, although it caused no apparent harm to the host (carrier), unless during the time of an acute upper respiratory infection, when pneumonia ensued. When these children from the nursery were transferred to a hospital ward they spread this pneumococcus (type 14) throughout the medical ward, infecting most of the children at one time or another. It was possible to anticipate the pneumonia since frequently the organisms were cultured in advance of the onset of the illness in those who were carrying the strain. The author

concluded that a virulent strain of pneumococcus may enter a community, permeate it and invade many individuals, and linger for a considerable time without causing any apparent harm, that is, until acute virus infections reduce the resistance of the carrier, thereby precipitating pneumonia.[9]

Studies involving the hemolytic streptococcus have been made by Loosli and his associates, in which the matter of contamination of the environment by the hemolytic streptococcus, and the spread of hemolytic streptococcal infection in army barracks, was observed.[10] It was concluded from these studies that attention had to be paid to "secondary reservoirs" as possible sources for the spread of infection due to this organism. Cultures taken simultaneously from barrack personnel as well as from the "secondary reservoirs" (bedding, dusts, wearing apparel, etc.) revealed a definite correlationship between the pharyngeal cultures and those of the reservoirs. In the barracks in which the majority of the positive bed, dust and air cultures showed the same type of streptococcus, the same type was most prevalent in the positive nose and throat cultures of the barrack personnel. It was indicated from observations of epidemics of sore throats that this mode of spread, in addition to the many opportunities for direct contact with the contaminated environment, would seem to offer the most likely explanation for the observation that the barracks was the principal focus for the spread of respiratory tract infections due to streptococci among those studied.[11] It will be, therefore, logical to study as well the role that the dust, the bedding and the air within the household play in disseminating sino-respiratory infections, particularly of the lowgrade variety.

The role of sneezing, coughing and talking in the dissemination of the hemolytic streptococcus was investigated by Hamburger and Robertson and found of minor importance.[12] Of special interest and particularly germaine to this discussion is the observation reported by Loosli, Smith, Cline and Nelson on the transmission of streptococcal infections in an infant ward, in which the skin acted as a disperser.[13] The original source of the streptococcus (Group A—Type 33) was a six month old female infant with an infection of the skin superimposed on infantile eczema. She subsequently contaminated the ward and secondary infections occurred in other infants, as well as adults, resulting in infections in the throats, skin and wounds. It was believed that the mechanism involved spread of the infection from the skin disperser to the bedclothes, and then to the air and dust, thereby infecting infants, the attending personnel and visitors. More startling in its scope was the observation described by Colbeck[14] concerning a particularly resistant strain of staphylococcus aureus which was responsible for an epidemic which was so extremely difficult to control, that several hospitals within a city had to be closed. The organism was subsequently observed in carriers among the hospital staff. These infected new-born infants whose nose and throat became an important reservoir for infection, and which was subsequently passed to the mother's breasts. A high incidence of boils and other pyogenic infections were then observed, in the families of these patients after their

return home from the hospital. The same organism was likewise implicated in the observations reported by Kugelmas,[15] in which post natal infection of the salivary glands was observed toward the end of the first week of life in infants. These infants were of low weight, delicate physically, and were overrun with staphylococcus aureus in the nasal pharynx. It was noted that the mother of each infant was afflicted with acne, folliculitis or furunculosis.

Finke in his excellent studies of respiratory infections confirms the epidemologic role herein emphasized.[16] Although no confirmatory bacteriologic studies were made his statistical studies are convincing. Of 224 children observed with primary pneumonia 67.9 per cent gave a history of recurrent croup, bronchitis, asthmatic bronchitis and related conditions. Of these patients 12.5 per cent had previous episodes of pneumonia. In another study of 176 children with bronchopulmonary infection there was a family history of bronchopulmonary infection in 86.2 per cent of the cases; in 72.4 per cent the onset of the infection dated to infancy, which belies the common notion that respiratory infections in children begin with schooling. Of particular interest were his studies, paralleling the observations herein recorded, of two types of families living in a single housing unit. In 64 families in which bronchopulmonary disease was in evidence in one or more members of the family, there were 166 children with a history of pneumonia in 22.3 per cent of them. In sharp contrast in 99 families without bronchopulmonary disease only 4.9 per cent of 269 children gave a history of pneumonia—one fourth the incidence.

Finke concludes from his studies that chronic bronchopulmonary disease is a public health problem since it is communicable and preventable. This conclusion is corroborated by the evidence presented in this communication.

An experimental approach to the problem of the epidemiology of respiratory infections was undertaken by Kruger and his associates at the Naval Research Medical Unit No. 1.[17] Here an apparatus was developed in which air-borne infections were quantatively produced and studied. Small laboratory animals were exposed to an aerosol of infectious material under controlled methods, and the spread of infection was determined. In a further study from this group radio-active air-borne bacteria were introduced into the apparatus so that these tagged organisms could be followed in the respiratory tract, and it was concluded that approximately 30 per cent of the tagged organisms were in the respiratory tract, while 70 per cent were ultimately found in the gastrointestinal tract.[18]

The therapeutic approach in the face of repeated or chronic sino-respiratory infection, particularly in children, is therefore not only to treat the infection in the respiratory tract, with the proper antibiotics but also to search for and eradicate any "disseminators" in the skin, eye, etc. The search should be extended to other members of the family and hygienic measures instituted—particularly as to sharing of clothing, towels, handkerchiefs, etc., to prevent dissemination from one member of the family to the others. During an acute upper respiratory infection, or during an exacerbatim of a skin or eye infection special precautions, including

isolation should be instituted. The chronically ill patient must be protected from the carrier or carriers within the family.

Should these prophylactic measures fail, therapy with an autogenous vaccine may be useful in building the patient's immunity which is most desirable.

SUMMARY

1) Bacteriologic studies indicate that chronic sino-respiratory infections are contagious within the family group.

2) The hemolytic staphylococcus was frequently encountered in these studies.

3) Infections of the skin and eye in the patient and/or relative may act as a focus for infection and reinfection of the respiratory tract.

4) Public health measures for preventing the spread and recurrences of these illnesses are indicated in view of the great morbidity.

RESUMEN

1) Los estudios bacteriológicos indican que las infecciones sino-respiratorias, son contagiosas dentro del grupo familiar.

2) El estreptococo hemolítico, fué encontrado con frecuencia en estos estudios.

3) Las infecciones de la piel y del ojo en el enfermo y o en los parientes, puede actuar como foco de infección o de reinfección en el tracto respiratorio.

4) Están indicadas las medidas de salubridad pública para evitar la diseminación y las recurrencias de estas afecciones en vista de la gran morbilidad que tienen.

RESUME

1) Les études bactériologiques montrent que les infections chroniques sino-respiratoires sont contagieuses au sein du groupe familial.

2) Le staphylocoque hémolytique fut fréquemment trouvé dans ces recherches.

3) Les atteintes de la peau et de l'oeil chez le malade et (ou) ses parents peuvent agir comme foyer d'infection ou de réinfection de l'arbe respiratoire.

4) Des mesures de prophylaxie contre la dissémination et les récidives de ces affections sont indiquées.

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Teaching Chest Disease

CLASS SESSION: HISTOPLASMOSIS

THEODORE H. NOEHREN, M.D., F.C.C.P.
Buffalo, New York

Those of us who have followed the reports of the United States Public Health Service teams working on histoplasmosis have been fascinated by their detective-like exposé of this disease. From the original observation of Palmer that a sizeable percentage of calcification on chest roentgenograms is not associated with tuberculin skin sensitivity, through the various processes of narrowing their observations to the areas of endemic histoplasmosis, and finally the demonstration of previously unsuspected clinical states of this disease, it has been a dramatic demonstration of deductive clinical and epidemiological research.

This whole drama can effectively be recapitulated in an hour's class session.

Using the Socratic method, whereby members of the class are encouraged to reason this thing out as a group exercise, the problem is started by making Palmer's original observation[1] that all pulmonary calcification may not be tuberculous. Films to demonstrate this are easily available today. As a matter of fact, we have used the chest roentgenograms of several class members as clinical material to initiate the discussion.

The second step to consider is the large scale skin testing of student nurses in different cities throughout the United States[2] which focused the attention on the endemic areas, especially the Mississippi Valley. Following this Furcolow and Mantz[3] skin tested almost 17,000 school children in Kansas City, Missouri to demonstrate the early age at which histoplasmosis sensitivity is contracted. Their next step, the mass chest roentgenograms of 16,000 school children in Kansas City, Missouri, revealed 72 symptom-free cases with combined pulmonary infiltration and positive histoplasmin skin tests.[4] Reproduction on slides of some of these cases, as illustrated in their reports, are valuable at this point.

The class generally has little difficulty in suggesting the next procedure which was the confirmation by culture of the organism from 10 of these cases, whose clinical pictures run the gamut of symptom-free infiltrates to fatal systemic disease. Again slide reproductions of some of these cases reported by Bunnell and Furcolow[5] create considerable interest.

At some point in these slides, generally at the end, the roentgenogram of a patient with pulmonary tuberculosis is unexpectedly thrown in to emphasize the similarity of these two disease infiltrates. This, supposedly,

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invites their future differential concern for both diseases when pulmonary infiltration is discovered. It also emphasizes the importance of positive confirmatory diagnosis in pulmonary infections.

It is a logical next-step to consider, in summary, the various forms this disease can present. On the basis of the slides already presented, the class has little difficulty reconstructing Furcolow's differentiation of generalized from local types of histoplasmosis, with the three subdivisions of the latter: nodular, pneumonic, and hilar node involvement. The relative ratio of each can be added from the more recent reports of over 100 cases by this same group.

Finally, we have been able to present one of our university students who contracted the disease in an endemic area, as a symptom-free case. Figures from our own hospital are also added to provide perspective on the relative infrequency of the disease in that area.

We feel this teaching approach has several advantages to recommend it. A class exercise in our experience is infinitely more stimulating than lectures per se. Usually enough in the group have some idea of histoplasmosis or the Public Health research in this field to add the catalyst to such a session. It is also a method of giving credit and insight to the work of the United States Public Health research teams.

Also, we hope that this demonstration of a disease which was known since the time of Darling in 1906 and can exist in our midst without definition for over 30 years, can encourage students to possibilities in this field. Finally, it is a bit of medical history which we hope may provide some of the background and inspiration which our clinical teaching needs today.

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Editorial

THE TURNING POINT

"It seems completely illogical not to treat an infectious disease at the earliest possible moment." "The tuberculin test serves two important functions; properly used, it tells us not only that an infection has taken place, but *when*, and perhaps even *where* that infection occurred." "Now that we have potent, inexpensive and easily taken antibiotics against the tubercle bacillus, every effort should be made to identify the moment of infection, the time of conversion of the tuberculin test, so that treatment may be started."

The general recognition of these facts so rightly stated by James J. Waring in this issue of *Diseases of the Chest* may well be the turning point in the whole tuberculosis eradication movement. This is exactly the principle upon which veterinarians have worked and by which they have achieved such phenomonal success.

When safe methods of administering tuberculin were announced by Pirquet (1907), Mantoux (1908), and Lautier (1908), it was observed that the majority of children and young adults who reacted appeared well, conventional physical examination was unrevealing, and x-ray film inspection, when used, rarely brought to view any significant abnormality.

Only the occasional individual who reacted to tuberculin had manifestations of illness and lesions were located by physical examination, including x-ray inspection. It was promptly deduced that a high percentage of these young individuals were infected, but only 1 or 2 per cent had the disease. Thus, a sharp dividing line was drawn between infection and disease. It was thought that those who had only infection walked within a charmed circle of safety as far as present or subsequent disease was concerned. Indeed, many physicians believed and taught that tuberculous infection "without disease" was an ideal situation for the individual. This concept became so implanted that, despite the subsequent accruement of overwhelming evidence of its erroneousness, it is still quoted and taught.

Ghon's pathological findings alone should have caused complete abandonment of this concept. In the early part of the second decade of this century, he meticulously examined the bodies of 184 persons dead from nontuberculous conditions, and in whom during life there was no evidence of tuberculosis, except the tuberculin reaction. He found tuberculous lesions in every body and commented upon the extremely small size of many of them. The minuteness of primary tuberculous lesions had previously been emphasized by pathologists as early as about 1876 when Hervouet, a student of Parrot, stressed with what care post-mortem examinations must be done as some primary tuberculous foci scarcely exceed the size of a pin's head. Kuss, in 1898, pointed out that primary tuberculous lesions could not be demonstrated clinically. He described them as varying from the size of a hazel nut to the head of a pin. Thus, there is little wonder that in the past and at present so relatively few lesions of primary tuberculosis complexes are located in the bodies of tuberculin reactors during life.

The vast experience of veterinarians, beginning with Gutman, Russia; Bang, Denmark; Pearson, Pennsylvania; and Russell, Wisconsin, in the early 90's and since confirmed almost four million times in the United States, alone, provided incontroversible evidence that tuberculous lesions are present in animals which react characteristically to tuberculin.

The concept of a sharp dividing line between infection and disease was again completely broken down when longitudinal studies revealed that an

alarming number of infected persons apparently normal in other respects later developed clinical lesions. So many, in fact, that it has been stated that persons infected with tubercle bacilli walk within the circle where all the illness and death occur from this disease.

The only two phases of present day examination whose results coincide are the tuberculin test and carefully done necropsies. Nothing else is sufficiently refined to establish the presence of primary tuberculosis complexes in the majority of persons and animals who have them. Individuals who react characteristically to tuberculin have tuberculosis as certainly as those ill or dead from the disease. The difference is one of evolution of lesions.

Most tuberculosis work in the past has consisted of following the great armies of tubercle bacilli. We have usually been years, and often decades, behind trying to find where they have left contingents and attempting to repair the damage. We have come upon these contingents after their hosts were sick, were liberating new armies of tubercle bacilli or possessed lesions so large as to be demonstrable by x-ray shadows they cast. Infrequently have attempts been made to spearhead the vast armies of tubercle bacilli. Rarely have we been on the job ahead of these armies.

Although in a few places noteworthy accomplishments have been achieved against tuberculosis, progress everywhere has been far too slow. In fact, there now exist vast populations in the world where the armies of tubercle bacilli have met with almost no opposition for the past 7,000 years. Even in areas including Scandinavian countries and the United States, where much has been accomplished, there is no single locality where the workers have travelled one-half the road to the eradication goal.

Requisites for successful control and eradication of any disease are (1) a specific test for its detection soon after it begins and (2) a specific method of treatment. Little progress was made in the control of syphilis until tests were available to find those persons whose tissues had been invaded with Spirocheta pallida. Drugs were produced to destroy those organisms. Although we have had a safe specific test for the detection of tubercle bacillus invasions for almost 50 years and the connotation of such invasions have been well understood for several decades, we have until recently lacked drugs that would effectively suppress and possibly destroy these organisms. Hence, the fatalistic concept pertaining to primary infections and the attempts to brush away their significance and even to regard them as assets to future health.

Now that drugs are available which so well suppress tubercle bacilli and possibly may in combination ultimately destroy them, one finds difficulty in disagreeing with Waring that these drugs should be administered promptly following the initial invasion. At that time, lesions of developing primary complexes are so small and vascular that all tubercle bacilli should be reached by drugs in the blood stream.

The only known method of determining promptly and accurately when invasions with tubercle bacilli have occurred is the appearance of sensitivity of tissues to tuberculo-protein. This important information can be obtained only by testing individuals periodically with tuberculin and finding those who convert from nonreactors to reactors. Except for an insignificant number of babies born with congenital tuberculosis, most of whom are stillborn or die soon after delivery, infants throughout the world are born free from tubercle bacilli and hence at birth do not react to tuberculin.

If the tuberculin test is administered to all babies at the age of approximately one month and every few months thereafter, those who become infected can be found when immediate treatment would be expected to be more efficacious than at any subsequent time in their lives. This applies

not only to infants, but also to persons of all ages. This simply means that everyone, regardless of age, must be tested with tuberculin and all non-reactors re-tested periodically to insure prompt recognition of every invasion. In this manner, we meet rather than follow the armies of tubercle bacilli and prevent destruction of tissues and perpetuation of their contingents.

Wherever such universal testing is done, many will be found, particularly in the upper age brackets, who are reactors on the initial test. For the majority of them we have arrived too late, since the lesions of primary complexes as well as reinfection implantations, which may have already occurred, have such decreased vascularity that one could hardly expect to destroy all of their tubercle bacilli with any drug. However, knowing that each tuberculin reactor, regardless of age, may then have or may subsequently develop reinfection implantations, we can watch and wait for their appearance, as manifested by illness or x-ray shadow-casting lesions. Prompt treatment of such lesions is now so effective that many of them can be brought under control and prevented from becoming contagious, while some already eliminating tubercle bacilli when found can be converted. The remainder must be isolated over varying periods of time. Unfortunately such persons are not cured, as other lesions already present may later evolve to demonstrable and destructive proportions. Therefore, all such treated individuals must have continued observation.

With the breaking down of old concepts and their replacement with well-established facts and prompt action has come the brightest future of all time for the ultimate eradication of tuberculosis. This goal is a long way off, but it is attainable.

J. Arthur Myers.

The President's Page

OUR COLLEGE CHAPTERS

This is the second in a series of messages concerning some of our College activities. The first article was published in the March issue of the Journal and I trust that you have had an opportunity to read it. I shall be more than pleased to have your reaction to these messages as well as your helpful suggestions.

The first chapter of the American College of Chest Physicians was organized by the members in Illinois, on May 21, 1940. This chapter was approved by the Board of Regents and was officially designated Chapter Number 1.

The following month, in New York City, members of the College from both New York and New Jersey petitioned the Board of Regents, then meeting in annual session, to be granted charters as College chapters. As both the New York State and the New Jersey Chapters were organized on the same date, June 10, 1940, it was agreed by representatives of these two states to draw lots to decide which chapter would have the distinction of being recognized as Chapter Number 2. New York drew the lucky number and officially became Chapter Number 2, and New Jersey was designated Chapter Number 3.

The first chapter of the College to be organized outside the United States was the Cuban Chapter which was formed on December 24, 1940, and approved by the Board of Regents at its Spring meeting. It became Chapter Number 4.

Thus, during the year 1940, began the organization of a system of College chapters which during the next decade was to spread throughout the world. Today we have 56 chapters officially chartered by the American College of Chest Physicians in 21 countries. This phase of our program is being expanded and additional chapters are now in the process of organization.

Each of our chapters is a self-sufficient unit, with its own officers and its own activities which have been correlated with the overall program of the College. Chapters throughout the world sponsor their own postgraduate courses, hold their own meetings annually, or more frequently, and present their own scientific programs covering the broad aspects of diseases of the chest. Many of the scientific programs presented by the chapters are of the same high calibre as the programs arranged for our annual and international meetings. In the United States, College chapters meet with the state and district medical societies and in some states sections on diseases of the chest have been established in the scientific assemblies of the state medical societies to make it possible for a greater number of physicians to attend the sessions. All chapters are required by the College By-laws to hold at least one meeting each year for the purpose of presenting a scientific program, electing officers and conducting the business of the chapter (Articles XI and XII).

The following lectures have been established by chapters, honoring prominent physicians: The Howard K. Lilienthal Lecture, New York State Chapter; the Charles M. Hendricks Lecture, Texas Chapter; the Paul A. Turner Lecture, Southern Chapter; and the J. J. Singer Lecture, California Chapter.

The officers of the chapters are encouraged to appoint committees which will work with the national councils and committees in carrying out the aims and objectives of the College. The College chapters are the proving grounds for future officials of the organization. Each member has an opportunity and should take advantage of this occasion to serve his chapter. By doing so, he will reap the greatest possible benefit from his College membership. Time invested in College activities will result in the satisfaction of having made a contribution to the advancement of our specialty. Let us keep the spirit and purpose of the founding fathers of the College ever before us as a guiding light.

Alvin E. Foster

20th Annual Meeting of the College

FAIRMONT HOTEL, SAN FRANCISCO

JUNE 17 - 20, 1954

In June, the 20th anniversary of the American College of Chest Physicians will be celebrated in San Francisco, California, one of the most interesting cities of the United States and a most appropriate setting for this special occasion. It is hoped that a great many members from all sections of the United States, Canada and nearby countries will be able to attend.

The Committee on Scientific Program, under the chairmanship of Dr. Edgar Mayer of New York City, has arranged a program of splendid scientific presentations, panel discussions, round table luncheons and motion pictures, as well as a diagnostic conference to be moderated by Dr. L. Henry Garland of San Francisco.

Some of the prominent speakers will be: Dr. Evarts A. Graham, St. Louis, Missouri, Bixby Professor Emeritus of Surgery, Washington University School of Medicine, who will give the first "J. J. Singer Lecture" sponsored by the California Chapter of the College; Dr. Ignacio Chavez, Mexico City, Director of the National Institute of Cardiology of Mexico; and Dr. Donato G. Alarcon, Mexico City, Regent of the College for Mexico, Professor of Medicine at the University of Mexico and Medical Director of the Sanatorio San Angel.

On Wednesday, June 16, a series of seminars will be presented and members are urged to avail themselves of this opportunity for postgraduate medical education in diseases of the chest. A list of the subjects to be presented and a registration form appear in this issue of the journal.

The oral and written examinations for Fellowship in the College will be held on Thursday, June 17, and the Board of Regents, Board of Governors, councils and committees will meet on that day. The Conference of College Chapter Officials will hold its regular luncheon meeting on Thursday, June 17. It is incumbent upon officials and members of national councils and committees to attend these important meetings. The Council on Hospitals will sponsor a special program on Thursday afternon and it will be to the interest of all physicians concerned with hospital administration to attend this meeting.

The formal Convocation for the awarding of Fellowship Certificates will take place at the Fairmont Hotel on Saturday, June 19. This ceremony will be followed by a cocktail party, sponsored by the Panray Corporation of New York City, and the Presidents' Banquet. The College Medal will be awarded at the banquet to a prominent scientist for meritorious achievement in the specialty of diseases of the chest. The California Chapter of the College will sponsor the remainder of the evening's entertainment.

The Ladies Reception Committee is preparing a fine social program and we trust that the ladies in your family will accompany you to San Francisco and take part in these activities.

On the following pages you will find the program for the 20th Annual Meeting of the College and at the end of the section there has been included a form for the reservation of tickets for many of the functions. It is urgently requested that reservations be made in advance to assure you of places at the various functions of your choice.

The Fairmont Hotel will be headquarters for the College meeting; however, there are not sufficient rooms at this hotel to accommodate all of the members of the College. San Francisco has a number of small, first class hotels and the Convention Bureau will make every effort to see that you are assigned comfortable accommodations.

SEMINARS

Fairmont Hotel, Wednesday, June 16

The following Seminars on Diseases of the Chest will be presented at the Fairmont Hotel on Wednesday, June 16. The Seminars have been accredited by the Board of Examiners for candidates for Fellowship in the College and preference will be given to members of the College.

The registration fee for each Seminar, which consists of a series of five lectures, is $7.50. Registration must be made in advance and accompanied by the tuition fee; seating capacity is limited and reservations will be accepted in the order in which they are received. A coupon for this purpose will be found on pages 473 and 474. Please indicate your preference by number.

Morning Sessions — 9:00 a.m. - 12:00 noon

AM-1 Cancer of the Lung.

Moderator: Seymour M. Farber, San Francisco, California.

"Physiological Aspects of Bronchogenic Neoplasms,"
Roger H. L. Wilson, San Francisco, California.

"Cytologic Aspects of Pulmonary Adenomatosis, Cancer of the Lung and Other Pulmonary Neoplasms,"
Mortimer A. Benioff, San Francisco, California.

"Industrial Aspects of Bronchogenic Neoplasms,"
Lester Breslow, San Francisco, California.

"Radiological Therapy of Carcinoma of the Lung,"
Melville L. Jacobs, Beverly Hills, California.

"Surgical Treatment of Cancer of the Lung,"
Gerald L. Crenshaw, Oakland, California.

AM-2 Infectious Diseases of the Chest.

Moderator: Charles M. Carpenter, Los Angeles, California.

"Viral Diseases of the Chest,"
A. F. Rasmussen, Jr., Los Angeles, California.

"Chemotherapy of Tuberculosis,"
H. Corwin Hinshaw, San Francisco, California.

"Segmental and Small Resections for Pulmonary Tuberculosis,"
Joseph Gordon, Albuquerque, New Mexico.

"Does Pulmonary Tuberculosis Continue to be a Chronic Disease Problem?"
Leo Tepper, Los Angeles, California.

"Mycotic Diseases of the Chest,"
David L. McVickar, Los Angeles, California.

Afternoon Sessions — 2:00 p.m. - 5:00 p.m.

PM-1 Cardiopulmonary Function and Cardiography.

Moderator: John J. Sampson, San Francisco, California.

"Pulmonary Function in Diseases of the Chest,"
Hurley L. Motley, Los Angeles, California.

"Pulmonary Circulation and the Pathological Physiology of the Leukemias,"
Howard R. Bierman, Los Angeles, California.

"Diagnosis of Cardiomegaly by Use of Artificial Gastric Air Bubble,"
Eliot Corday, Beverly Hills, California.

"Vectorcardiography,"
Bertram J. Allenstein, Los Angeles, California.

"The Clinical Application of Quinidine in the Treatment of Auricular Fibrillation,"
Samuel A. Weisman, Los Angeles, California.

PM-2 Surgical Treatment of Heart Disease.

Moderator: Morse J. Shapiro, Beverly Hills, California.

"Cardiopulmonary Angiography,"
Arthur Fisher, Duarte, California.

"Diagnosis, Physiology and Treatment of Rheumatic Fever and Rheumatic Heart Disease,"
Richard S. Cosby, Los Angeles, California.

"Surgical Treatment of Acquired Heart Disease,"
H. Brodie Stephens, San Francisco, California.

"Diagnosis and Management of Congenital Heart Disease in the Adult,"
Sidney S. Sobin, Beverly Hills, California.

"Diagnosis and Management of Congenital Heart Disease,"
Frank Dammann, Los Angeles, California.

SCIENTIFIC PROGRAM

The scientific sessions of the College will begin promptly as scheduled and it is requested that the audience be seated at least five minutes prior to the opening of the session.

Thursday, June 17

8:00 p.m. — Opening Scientific Session.

Remarks: Edgar Mayer, New York City,
Chairman, Committee on Scientific Program.

"J. J. Singer Lecture,"
Sponsored by the California Chapter, American College of Chest Physicians. Introduction by Alfred Goldman, Los Angeles, Calif.

"Remarks on the Etiology of Bronchogenic Carcinoma,"
Evarts A. Graham, St. Louis, Missouri.

PANEL ON RESEARCH PROBLEMS

Herman J. Moersch, Rochester Minnesota, *Chairman.*
Roy A. Wolford, Washington, D. C., *Co-Chairman.*

"The Hematological Role of the Lung,"
Howard R. Bierman, Duarte, California.

"Lung Biopsy in Diffuse Pulmonary Disease,"
Peter A. Theodos, Frank F. Allbritten, Jr. and
Robert L. Breckenridge, Philadelphia, Pennsylvania.
Discussor: Frank L. Gerbode, San Francisco, California.

"Physiological Effects of Exsufflation with Negative Pressure,"
Gustav J. Beck and L. Scarrone, New York City.
Discussor: Maurice S. Segal, Boston, Massachusetts.

"Mechanism of Cardiac Ascites—An Experimental Study,"
Ivan D. Baronofsky and Joseph L. Sprafka, Minneapolis, Minnesota.

"Bacteriophage Susceptibility of Variant Strains of BCG and Other Tubercle Bacilli,"
Seymour Froman, Irving Krasnow and Drake W. Will, Olive View, California.
Discussor: Emil Bogen, Olive View, California.

"Esophageal Motility Studies,"
N. C. Hightower, Temple, Texas.
Discussor: Charles F. Code, Rochester, Minnesota.

"Advances in the Surgical Alleviation of Congenital Pulmonic Stenosis,"
Henry T. Nichols and Daniel Downing, Philadelphia, Pennsylvania.
Discussor: Charles P. Bailey, Philadelphia, Pennsylvania.

Friday, June 18

9:00 a.m. — Physiologic Therapy and Function of Pulmonary Disease

Hurley L. Motley, Los Angeles, California, *Chairman.*
D. W. McCauley, Okmulgee, Oklahoma, *Co-Chairman.*

"The Microscopic Structure of the Lung,"
Vernon E. Krahl, Baltimore, Maryland.

"Mechanical Factors Governing Expiratory Obstruction of Air Flow,"
Howard Dayman, Buffalo, New York.
Discussor: Roger H. L. Wilson, San Francisco, California.

"The Clinical Use of Continuous Nebulization in Bronchopulmonary Disease,"
Robert Denton, Oakland, California.
Discussor: Paul C. Samson, Oakland, California.

"Treatment of Pulmonary Emphysema with Aerosolized Bronchodilators and Intermittent Positive Pressure Breathing,"
W. S. Fowler, H. F. Helmholz, Jr. and R. Drew Miller, Rochester, Minnesota.
Discussors: Robert H. Scherb, Bakersfield, California and
Reginald H. Smart, Los Angeles, California.

"Advances in Inhalational Therapy,"
Maurice S. Segal, Boston, Massachusetts.
Discussor: Reginald H. Smart, Los Angeles, California.

PANEL DISCUSSION

Alvan L. Barach, New York City, *Moderator*
Hylan A. Bickerman, New York City
James T. Duncan, Livermore, California
Burgess L. Gordon, Philadelphia, Pennsylvania
H. F. Helmholz, Jr., Rochester, Minnesota
James Kieran, Oakland, California
Edwin R. Levine, Chicago, Illinois

12:00 Noon — Round Table Luncheon Meetings (see pages 469 and 470).

2:00 p.m. — Cardiovascular Diseases

James H. Stygall, Indianapolis, Indiana, *Chairman.*
Maurice Campagna, New Orleans, Louisiana, *Co-Chairman.*

"Pulmonary Hypertension as an Important Factor in Cardiac Surgery,"
Ignacio Chavez, Mexico City, Mexico.

"Indications for Commissurotomy in Mitral Stenosis,"
George C. Griffith, Los Angeles, California.

"Newer Advances in the Treatment of Coronary Thrombosis,"
Arthur M. Master, New York City.

"The Treatment of Shock with Vasopressor Amines,"
John J. Sampson, San Francisco, California.

"The New Hypotensive Agents in High Blood Pressure,"
Robert W. Wilkins, Boston, Massachusetts.

"Aortic Stenosis, a Clinical Evaluation of Its Surgical Management (Report of 150 Cases),"
William Likoff, Donald Berkowitz, Clarence Denton,
Harry Goldberg and Atilio Reale, Philadelphia, Pennsylvania.

PANEL DISCUSSION

Arthur M. Master, New York City, *Moderator*
Ignacio Chavez, Mexico City, Mexico
George C. Griffith, Los Angeles, California
John J. Sampson, San Francisco, California
Robert W. Wilkins, Boston, Massachusetts

8:00 p.m. — Motion Picture Session on Diseases of the Chest

A program of recent films on diseases of the chest is being arranged by the Committee on Audiovisual Aids of the College and will be published in a future issue of *Diseases of the Chest*.

Saturday, June 19

10:00 a.m. — Symposium: Special Forms of Pulmonary Dust Diseases

Reginald H. Smart, Los Angeles, California, *Chairman*.
Carl H. Gellenthien, Valmora, New Mexico, *Co-Chairman*.

"Anthracosis,"
G. W. H. Schepers, Saranac Lake, New York.

"Diatomaceous Earth Pneumoconiosis,"
William H. Carnes, San Francisco, California.

"Asbestosis,"
Kenneth W. Smith, New York City.

"Siderosis,"
Robert Charr, Philadelphia, Pennsylvania.
Discussors: Louis L. Friedman, Birmingham, Alabama,
Oscar A. Sander, Milwaukee, Wisconsin, and
Arthur J. Vorwald, Detroit, Michigan

PANEL DISCUSSION

"Emphysema in Relation to Industrial Occupation"
Edgar Mayer, New York City, *Moderator*.

Clinical Aspects:	Marvin S. Harris, Los Angeles, California
Physiological Aspects:	Hurley L. Motley, Los Angeles, California
Pathological Aspects:	Philip C. Pratt, Saranac Lake, New York
X-ray Aspects:	Leo G. Rigler, Minneapolis, Minnesota
Therapeutic Aspects:	Reginald H. Smart, Los Angeles, California

12:00 Noon — Round Table Luncheon Meetings (see pages 469 and 470).

2:00 p.m. — Nontuberculous Diseases of the Chest

Arthur M. Olsen, Rochester, Minnesota, *Chairman*.
Carl C. Aven, Atlanta, Georgia, *Co-Chairman*.

"Supervoltage Therapy of Inoperable Bronchogenic Carcinoma,"
Hugh F. Hare, Los Angeles, California.
Discussors: Hirsch Marks, New York City,
Robert B. Stone, San Francisco, California.

"The Treatment of Pulmonary Blastomycosis,"
James D. Murphy, Timothy Takaro and James E. T. Hopkins,
Oteen, North Carolina.

"Respiratory Infections Due to Klebsiella Pneumoniae,"
Glenn M. Morris and J. Lewis Yates, Detroit, Michigan.

"Clinical Experience with Pneumoperitoneum in the Treatment of So-called Hypertrophic Emphysema,"
Andrew L. Banyai and Leon H. Hirsh, Milwaukee, Wisconsin.

"Is Survey Cancer of the Lung Curable?"
Katharine R. Boucot and Martin J. Sokoloff, Philadelphia, Pennsylvania.

"The Pulmonary Manifestations of Fibrocystic Disease of the Pancreas,"
Paul di Sant'Agnese, New York City.

3:30 p.m. — Diagnostic Conference,

L. Henry Garland, San Francisco, California, *Moderator*.

Sunday, June 20

9:00 a.m. — Tuberculosis

Donald R. McKay, Buffalo, New York, *Chairman*.
C. Lydon Harrell, Norfolk, Virginia, *Co-Chairman*.

"A Comparative Study on Conventional Therapy vs. Drugs Plus Surgery in Pulmonary Tuberculosis,"
Albert R. Allen, Guy E. Marcy and James K. Yu, Seattle, Washington.

"The Handling of the Poor Risk Patient with Pulmonary Tuberculosis with Reference to Antimicrobial Therapy—Pulmonary Function and Surgery,"
Albert Kukral, John B. Grow, Sidney H. Dressler and Gardner Middlebrook, Denver, Colorado.

"Long Time Antimicrobial Therapy Without Collapse—300 Cases Treated for One Year or Longer,"
W. J. Steininger and W. Leonard Howard, Northville, Michigan.

SUMMARY PRESENTATIONS

Harold G. Trimble, Oakland, California, *Moderator*.

"A Study of the Effects of Distrycin on Pulmonary Tuberculosis—Especially in Streptomycin or Dihydrostreptomycin Sensitive Patients,"
Harry Shubin, Charles A. Heiken, Allen Glaskin, Edward Pennes, Sushil Chakravarty and Franklin Rutberg, Philadelphia, Pennsylvania.

"A Pilot Study of Salizid, An Isonicotinic Acid Hydrazide Analogue,"
Sol Katz, Georges F. McCormick, Patrick B. Storey, Angel de Leon, Monroe J. Romansky and Edward E. Marshall, Jr., Washington, D. C.

"A Study of Tuberculosis Cavities,"
Oren A. Beatty, William Dowden, Stanislaus Jaudzems and A. Pakalns, Louisville, Kentucky.

"Detection of Tubercle Bacilli in Surgical Specimens Removed by Small Resections of the Lung,"
Alfred Goldman, W. J. Gyarfas, Fred S. Preuss, Ben Rosner, Milton Virshup, Clifford O. Bishop and Masaya Nishimura, Los Angeles, California.

"The Continuous Use of Antimicrobial Therapy in Excess of One Year in Patients with Pulmonary Tuberculosis,"
Daniel E. Jenkins, Houston, Texas.

"Massive Pulmonary Hemorrhage as a Surgical Emergency,"
Howell Randolph, Phoenix, Arizona.

PANEL DISCUSSION

"When do you NOT Use Excision Therapy in Pulmonary Tuberculosis"

David H. Waterman, Knoxville, Tennessee, *Moderator*
Donato G. Alarcon, Mexico City, Mexico
Emil Bogen, Olive View, California
Albert C. Daniels, San Francisco, California
Chevalier L. Jackson, Philadelphia, Pennsylvania
Richard H. Overholt, Brookline, Massachusetts
Sidney J. Shipman, San Francisco, California

12:00 Noon — Round Table Luncheon Meetings (see pages 469 and 470).

2:00 p.m. — Surgery

J. Winthrop Peabody, Washington, D. C., *Chairman*.
James M. Odell, The Dalles, Oregon, *Co-Chairman*.

"Bronchiolar Carcinoma,"
Richard H. Overholt, William A. Meissner and J. Ernest Delmonico, Jr., Boston, Massachusetts.

"Results of Radical Pneumonectomy for Carcinoma of the Lung,"
John L. Pool, New York City.
Discussor: John F. Higginson, Portland, Oregon.

"Surgical Treatment of Pulmonary Coccidioidomycosis,"
Bert H. Cotton and J. W. Birsner, Los Angeles, California.

"Regressive Giant Bullous Emphysema in the Adult,"
Donato G. Alarcon, Mexico City, Mexico.

"Further Experiences with Atrio-Septo-Pexy in the Closure of Interatrial Septal Defects,"
Charles P. Bailey, Philadelphia, Pennsylvania.

PANEL DISCUSSION

"Diagnostic Problems in Thoracic Surgery"

Herbert C. Maier, New York City, *Moderator*
Alfred Goldman, Los Angeles, California
Donald L. Paulson, Dallas, Texas
Paul C. Samson, Oakland, California

ROUND TABLE LUNCHEONS

Friday, June 18

A-1 "The Esophagus, a Frequently Overlooked Organ,"

Abel Froman, Chicago, Illinois; Chevalier L. Jackson, Philadelphia, Pennsylvania; George S. McReynolds, Galveston, Texas; Paul C. Samson, Oakland, California.

Moderator: Albert H. Andrews, Jr., Chicago, Illinois.

A-2 "The Evaluation of Low Calorie and Low Fat Diets in Heart Disease,"

Arthur Bloomfield, San Francisco, California; Francis L. Chamberlain, San Francisco, California; Simon Dack, New York City; John Gofman, San Francisco, California.

Moderator: David A. Rytand, San Francisco, California.

A-3 "Cancer of the Lung,"

Duane Carr, Memphis, Tennessee; William A. Hudson, Detroit, Michigan; Russell V. Karlen, San Mateo, California; William B. Leftwich, Oakland, California; Richard H. Overholt, Brookline, Massachusetts.

Moderator: William L. Rogers, San Francisco, California.

A-4 "Indications for Pulmonary Surgery in Infancy and Childhood,"

Lyman A. Brewer, Los Angeles, California; Lloyd B. Dickey, San Francisco, California; John S. Harter, Louisville, Kentucky; Mark Ravitch, New York City.

Moderator: Jay Arthur Myers, Minneapolis, Minnesota.

A-5 "Chemotherapy,"

Edward Dunner, St. Louis, Missouri; Charles A. Heiken, Philadelphia, Pennsylvania; Karl H. Pfuetze, Chicago, Illinois; William E. Van Fleit, Atlanta, Georgia; Thomas B. Wiper, Belmont, California.

Moderator: H. Corwin Hinshaw, San Francisco, California.

A-6 "Treatment of Pneumoconiosis,"

Louis L. Friedman, Birmingham, Alabama; James Kieran, Oakland, California; Edward Lebovitz, Pittsburgh, Pennsylvania; Joseph Martin, Elkins, West Virginia.

Moderator: Peter A. Theodos, Philadelphia, Pennsylvania.

Saturday, June 19

B-1 "The Lymphomas,"

Franz Buschke, Seattle, Washington; Clyde Dawe, Rochester, Minnesota; David J. Dugan, Oakland, California.

Moderator: Byron E. Hall, San Francisco, California.

B-2 "Cor Pulmonale,"

Ellen Brown, Benson B. Roe, Arthur Selzer, Roger H. L. Wilson, San Francisco, California.

Moderator: Alfred Goldman, St. Louis, Missouri.

B-3 "Home Care of Tuberculosis,"

J. Lloyd Eaton, Oakland, California; Jerome Flance, St. Louis, Missouri; Carl C. Kuehn, Pittsburgh, Pennsylvania; George Martin, Pittsburgh, Pennsylvania; Andrew Meyer, Oakland, California.

Moderator: Edward W. Hayes, Monrovia, California.

B-4 "Obstetrics and Tuberculosis,"

Philip Arnot, San Francisco, California; John P. M. Black, Olive View, California; George F. Calvin, Oakland, California; Henry Dorffman, New York City; Irving Willner, Newark, New Jersey.

Moderator: Otto L. Bettag, Chicago, Illinois.

B-5 "Surgical Treatment of Pericardial Lesions,"

Frank L. Gerbode, San Francisco, California; William Likoff, Philadelphia, Pennsylvania; Donald L. Paulson, Dallas, Texas; Arthur Twiss, Oakland, California.

Moderator: John F. Briggs, St. Paul, Minnesota.

B-6 "Use of Pulmonary Function Studies in Disability Evaluation and Management of Pneumoconiosis,"

Ross C. Kory, Wood, Wisconsin; Hurley L. Motley, Los Angeles, California; Charles A. Webster, San Francisco, California.

Moderator: George R. Meneely, Nashville, Tennessee.

Sunday, June 20

C-1 "The Use of Radioisotopes in Pulmonary Disease,"

Hardin Jones, Berkeley, California; Morris Levine, Denver, Colorado; R. Drew Miller, Rochester, Minnesota; Bernard Roswit, Bronx, New York.

Moderator. John H. Lawrence, Berkeley, California.

C-2 "The Indications for Surgery in Heart Disease,"

Richard S. Cosby, Los Angeles, California; Herbert C. Maier, New York City; Mary Olney, Saul Robinson, San Francisco, California.

Moderator: Frank L. Gerbode, San Francisco, California.

C-3 "Intermittent Positive Pressure Breathing,"

Burgess L. Gordon, Philadelphia, Pennsylvania; Edwin R. Levine, Chicago, Illinois; W. S. Fowler, Rochester, Minnesota; Maurice S. Segal, Boston, Massachusetts.

Moderator: Reginald H. Smart, Los Angeles, California.

C-4 "What About the Heart?"

Hans H. Hecht, Salt Lake City, Utah; Fay A. LeFevre, Cleveland, Ohio; Aldo Luisada, George A. Hellmuth, Chicago, Illinois.

Moderator: Myron Prinzmetal, Los Angeles, California.

C-5 "ACTH and Cortisone in Pulmonary Diseases,"

Alvan L. Barach, New York City; Ethan A. Brown, Boston, Massachusetts; Smith Freeman, Chicago, Illinois; Joseph Mindlin, Downey, Illinois; Bram Rose, Montreal, Canada.

Moderator: Laurance W. Kinsell, Oakland, California.

C-6 "Surgery in Aortic Disease,"

Charles P. Bailey, Philadelphia, Pennsylvania; Charles A. Hufnagel, Washington, D. C.; Hobart Rogers, Oakland, California; H. Brodie Stephens, San Francisco, California.

Moderator: H. Easton McMahon, New York City.

ADMINISTRATIVE SESSIONS

American College of Chest Physicians

Wednesday, June 16

8:00 a.m. — Registration

Registration for the annual meeting of the College will open at 8:00 a. m. on Wednesday, June 16, on the Lobby Floor of the Fairmont Hotel. There will be registration desks for members, guests and ladies, as well as a desk where tickets for the various College functions may be obtained. Please register early and obtain all tickets at the time of registration. Admittance to the scientific sessions will be by badge only.

2:00 - 4:00 p.m. — Meeting of the Executive Council

Thursday, June 17

The Board of Regents, Board of Governors, councils and committees of the College will meet on Thursday, June 17.

Oral and written examinations for Fellowship in the College will be held on Thursday, June 17, the written examinations in the morning and the oral in the afternoon.

At 12:00 noon on Thursday, there will be a luncheon meeting of the Conference of College Chapter Officials, including the Board of Regents, Board of Governors, council and committee members. Certificates of Merit will be awarded to Past-presidents of College Chapters and guest speakers will be present.

A special program sponsored by the Council on Hospitals of the College will be presented on Thursday afternoon to which all interested physicians are invited. A paper will be presented on the subject "Changing Trends in Tuberculosis Hospitals" and following this there will be a question and answer period on the general subject of tuberculosis institutional problems. A panel of experts will be present to answer all questions.

Saturday, June 19

9:00 - 10:00 a.m. — Administrative Session

Report of the Historian
Report of the Treasurer
Report of the Executive Director
Report of the Committee on Nominations
Election of Officers

Sunday, June 20

4:00 - 5:00 p.m. — Meeting of the Board of Regents

SOCIAL ACTIVITIES

Saturday, June 19

6:00 - 7:00 p.m. — Annual Convocation (Formal)
7:00 - 7:30 p.m. — Cocktail Party (sponsored by Panray Corporation)
7:30 - 9:30 p.m. — Annual Presidents' Banquet
9:30 p.m. — Dancing and Entertainment
Sponsored by the California Chapter of the College

Social activities for the ladies are being planned and will be announced at a later date.

TECHNICAL EXHIBITS

American College of Chest Physicians

American Cystoscope Makers, Inc.
New York, New York

Barnes-Hind Laboratories, Inc.
San Francisco, California

V. Ray Bennett and Associates, Inc.
Los Angeles, California

Ciba Pharmaceutical Products, Inc.
Summit, New Jersey

Warren E. Collins, Inc.
Boston, Massachusetts

Joseph K. Dennis Company
Chicago, Illinois

J. H. Emerson Company
Cambridge, Massachusetts

E. Fougera and Company
New York, New York

Grune & Stratton, Inc.
New York, New York

Imported Specialties & Supplies, Inc.
Boonton, New Jersey

Levinthal Electronic Products, Inc.
Redwood City, California

Linde Air Products Company
New York, New York

Mine Safety Appliances Company
Pittsburgh, Pennsylvania

The Panray Corporation
New York, New York

Chas. Pfizer and Company
Brooklyn, New York

George P. Pilling & Son Company
Philadelphia, Pennsylvania

Production Foundry Company
Oakland, California

J. B. Roerig & Company
Chicago, Illinois

Spencer, Inc.
New Haven, Connecticut

Annual Meeting, American Medical Association

The American Medical Association will hold its annual meeting in San Francisco, June 21 through 25, 1954. The Section on Diseases of the Chest in the AMA will present interesting scientific programs on Wednesday, Thursday and Friday, June 23, 24 and 25, from 9:00 a.m. to 12:00 noon. There will also be a group of excellent scientific exhibits in the Section on Diseases of the Chest on display at the Civic Auditorium in San Francisco.

OFFICERS OF THE SECTION ON DISEASES OF THE CHEST

J. Arthur Myers, Minneapolis, Minnesota, Chairman
Andrew L. Banyai, Milwaukee, Wisconsin, Vice Chairman
John F. Briggs, St. Paul, Minnesota, Secretary
Hollis E. Johnson, Nashville, Tennessee, Delegate
Edward W. Hayes, Monrovia, California, Alternate Delegate
Edwin R. Levine, Chicago, Illinois,
Representative to the Scientific Exhibit.

INFORMATION FORM

EXECUTIVE OFFICES
AMERICAN COLLEGE OF CHEST PHYSICIANS
112 East Chestnut Street, Chicago 11, Illinois

I am planning to attend the annual meeting of the College in San Francisco, June 17-20, 1954, and will be accompanied by:

.....

I have reservations at the Hotel .....

Arrival date ..... Departure date .....

I am enclosing my check in the amount of $ ..... for reservations as listed on the reverse side of this form.

Remarks .....

Name .....

Address .....

City ..... State .....

QUESTIONS, PLEASE!

Participation in the panel discussions of the scientific program is encouraged. Will you therefore please submit below any questions you would like to have answered:

.....

.....

.....

.....

.....

.....

.....

Do you wish to submit films for the diagnostic conference? .....

RESERVATION FORM

Seminars, Wednesday, June 16 **($7.50 each)**

MORNING SESSIONS	AFTERNOON SESSIONS
9 a.m. - 12 noon	2:00 - 5:00 p.m.
First choice A.M.	First choice P.M. .....

Please indicate choice by number as listed in program.

Round Table Luncheons **($3.50 each)**

	Friday, June 18	Saturday, June 19	Sunday, June 20
First choice	A-	B-	C- .....
Second choice	A-	B-	C- .....
Third choice	A-	B-	C- .....

Please indicate choice by number as listed in program.

Luncheon, Conference of College Chapter Officials **($3.50 each)**

I wish to reserve ..... tickets for the luncheon meeting of the College Chapter Officials, Board of Regents, Board of Governors, Councils and Committees, Thursday noon, June 17.

Presidents' Banquet, Saturday, June 19 **($6.50 each)**

I wish to reserve ..... tickets for the Presidents' Banquet, Saturday, June 20. (Price includes cocktails, dinner, dancing and entertainment.)

NOTE: Please make checks payable to *The American College of Chest Physicians*. Checks must accompany all requests for reservations and will be accepted in the order in which they are received. All tickets will be held for pick-up at the College Registration Desk, Fairmont Hotel.

Ammendments to the By-Laws

At the semi-annual meeting of the Board of Regents of the College, held in St. Louis, Missouri, on Monday, November 30, 1953, the Committee on College By-Laws presented the following amendments to the Board for consideration. The proposed changes were approved by the Board of Regents and in accord with Article XIII of the By-Laws are published herein and will be presented to the Fellowship of the College at the annual meeting in San Francisco on Saturday, June 19, for adoption or rejection.

PROPOSE CHANGES

It is recommended that the College By-Laws be amended to read that all applicants for membership be admitted to either Associate Fellowship or Associate Membership, with the exception of those candidates who are admitted directly to full Fellowship without examination.

It is recommended that the office of Assistant Treasurer be added to the list of officers which is presented annually by the Committee on Nominations. (Article X, Section 8, page xvi.)

It is recommended that the Chairman of the Council on International Affairs be appointed by the President to serve for a period of two years, as stated in the By-Laws, and that the remainder of that sentence, i.e., "and is to be from the country where the International Congress on Diseases of the Chest is to be held" be removed from the By-Laws. (Article XII, Section 5, page xix.)

Carl H. Gellenthien, Valmora, New Mexico, *Chairman*
Hollis E. Johnson, Nashville, Tennessee
Henry W. Leetch, Saranac Lake, New York
Robert E. Schwartz, Hattiesburg, Mississippi
Walter E. Vest, Huntington, West Virginia.

College Chapter News

LOUISIANA CHAPTER

In New Orleans on February 15, members of the College formed the Louisiana Chapter, the fifty-sixth chapter of the College. Dr. Alvis E. Greer, Houston, Texas, President of the College, and Dr. J. Winthrop Peabody, Washington, D. C., Past-president and Chairman of the Council on Postgraduate Medical Education, spoke briefly before the group. The following officers were elected:

Maurice Campagna, New Orleans, President
P. R. Gilmer, Shreveport, Vice-President
Lawrence H. Strug, New Orleans, Secretary-Treasurer
Isadore L. Robbins, New Orleans, Executive Committee
Thomas Black, Alexandria, Executive Committee.

CALIFORNIA CHAPTER

The California Chapter will meet on May 8 at the Biltmore Hotel in Los Angeles, at the time of the annual meeting of the California Medical Association. The business meeting will begin at 12:30 p.m., after which the following scientific program will be presented:

"The Medical Surgical Team in the Treatment of Mitral Stenosis,"
Joseph F. Sadusk, Jr., Oakland.
Discussor: David J. Dugan, Oakland.

"Personality and Tuberculosis,"
Barbara M. Stewart, Ph.D. and Shalom E. Vineberg, Ph.D., San Fernando.

"Minifilm Utilization After a Chest Survey,"
Blanch Perkins and Emil Bogen, Olive View.

"Management of Diaphragmatic Hernia in the Aged,"
Byron H. Evans and Joseph B. Ford, Jr., Los Angeles.

"Diagnostic Use of Pneumoperitoneum in Non-Tuberculous Diseases,"
Harold G. Trimble and William B. Leftwich, Oakland.

"Bronchial Diseases in Childhood Tuberculosis,"
Henry J. Rubin and Marvin S. Harris, Los Angeles.

The annual "J. J. Singer Lecture" which has been established by the chapter will be presented at the time of the 20th Annual Meeting of the College in San Francisco, on June 17. Dr. Evarts A. Graham, St. Louis, Missouri, will give the lecture and the title of his presentation is "Remarks on the Etiology of Bronchogenic Carcinoma."

ILLINOIS CHAPTER

The Illinois Chapter will hold its Annual Meeting in conjunction with the meeting of the Illinois State Medical Society, on May 20 at the Hotel Sherman in Chicago. The following program will be presented:

"Modern Trends in Resectional and Collapse Surgery of Pulmonary Tuberculosis,"
Robert T. Fox and William M. Lees, Chicago.

"Pulmonary Fibrosis,"
George C. Turner, Chicago.

Annual Lecture
"Cancer of the Lung; Difficulties in Early Diagnosis,"
Alton Ochsner, New Orleans, Louisiana.

A luncheon and business meeting will follow the scientific session.

KANSAS CHAPTER

The Kansas Chapter will present an x-ray conference and panel discussion at the Hotel Jayhawk in Topeka, May 4. Dr. C. F. Taylor, Norton, will be moderator. Panel members are: Homer L. Hiebert, Topeka; Martin J. FitzPatrick, Kansas City; and Arthur Ashmore, Wichita. A dinner will follow.

NEW ENGLAND CHAPTER

The annual meeting of the New England Chapter, comprising the states of Maine, Massachusetts, Vermont, New Hampshire, Connecticut and Rhode Island, will be held at the Deaconess Hospital in Boston, May 19. Part of the meeting will be devoted to a clinical pathological conference.

NEW JERSEY CHAPTER

The New Jersey Chapter will hold its annual meeting on May 19 at the Chalfonte-Haddon Hall, Atlantic City. Guest speaker will be Dr. Burgess L. Gordon, Philadelphia, Pennsylvania, who will speak on "The Expanding Field in the Study and Treatment of Chronic Pulmonary Diseases."

NEW YORK CHAPTER

The annual dinner meeting of the New York Chapter will be held at the Hotel Statler, New York City, on May 13, at which time the fourth "Howard Lilienthal Lecture" will be presented. The following program of the Section on Chest Diseases of the Medical Society of the State of New York will be presented on May 14:

"Silent Mediastinal Pathology Discovered on Routine Chest X-ray Studies,"
Ida Levine and Henry Greenfield, Brooklyn.
Discussor: John Evans, New York City.

"Fungus Disease of the Lungs,"
David T. Smith, Durham, North Carolina.
Discussor: Rhoda Benham, New York City.

"Restoration of Vascular Continuity by Homologous Grafts,"
Jere W. Lord, Jr., New York City.
Discussor: Arthur H. Blakemore, New York City.

"Treatment of Pulmonary Tuberculosis" (Panel Discussion)
Frederick Beck, Raybrook; Nicholas D'Esopo, West Haven, Connecticut; Jacob Rogoff, Brooklyn; and Edward Sawtelle Welles, Saranac Lake.
Moderator: Charles E. Hamilton, Brooklyn.

"Silent Chest Diseases Discovered by Chance Chest X-ray,"
Aaron D. Chaves, New York City.

OKLAHOMA CHAPTER

The Oklahoma Chapter will meet at the Municipal Auditorium in Oklahoma City, May 9. Dr. Allen Greer, Oklahoma City, will preside at the scientific session at which time the following papers will be presented:

"Clinical Findings of an Unusual Case," Felix R. Park.
"Cor Pulmonale," C. S. Lewis.

Dr. R. M. Shepard, Sr., Tulsa, President of the chapter, will moderate an x-ray conference to be followed by the business session conducted by Dr. D. W. McCauley, Okmulgee, Governor of the College for Oklahoma.

TEXAS CHAPTER

The Texas Chapter will hold its annual meeting in San Antonio, May 2, in conjunction with the meeting of the state medical association. Dr. John S. Chapman, Dallas, has arranged the following program:

"Benign Lesions of the Esophagus,"
C. O. Patterson, Dallas.

"A Study of Pneumonias in Older Males in Relation to Carcinoma,"
D. O. Shields, et al, McKinney.

Charles M. Hendricks Lecture,
"Carcinoma of the Esophagus,"
William A. Hudson, Detroit, Michigan, President-elect,
American College of Chest Physicians.

Luncheon and business meeting.

"Vitamin B-12 in the Treatment of Peripheral Neuritis Associated with Isoniazid Therapy,"
A. N. Longfield, Galveston.

"A Study of Adjustment to Prolonged Hospitalization for Tuberculosis: I. Prediction of Criteria Groups,"
L. J. Moran, Houston.

X-ray Conference,
Moderator: E. F. Lyon, Jr., San Antonio.

College News Notes

Dr. Joseph C. Placak, Cleveland, Ohio, was presented with an oil portrait in honor of his services in the field of tuberculosis by the Antituberculosis League of Cleveland and Cuyahoga County on January 29. Dr. Placak is a past-president of the College. In accepting the portrait, Dr. Placak said, "It's a long fight and a continuous fight and we are sadly deluding ourselves if we think that tuberculosis is merely a peril of the past."

Dr. M. Eugene Flipse, formerly of Miami, Florida, has been appointed Head of the Chest Service at the U. S. Naval Hospital, Bethesda, Maryland.

Dr. William A. Hudson, Detroit, Michigan, President-elect of the College, spoke before the student body at Bethany College, Bethany, West Virginia, February 25, on "The Background and Development of the Art and Science of Medicine," and on "The Place of Basic Sciences in the Field of Medicine and Surgery" before the pre-medical students.

Drs. Edwin R. Levine and Abel Froman have entered into a partnership with offices in Chicago, Illinois.

ANNOUNCEMENT

A request has been received from a large mission sanatorium in India for many back numbers of the College journal, *Diseases of the Chest*, from 1950 to 1953, inclusive. Donations of these issues would be greatly appreciated. For details, please communicate with Dr. Douglas N. Forman, Secretary, Christian Medical Council for Overseas Work, Room 1111, 156 Fifth Avenue, New York 10, New York.

Obituary

CHARLES M. HENDRICKS

1878 - 1953

CHARLES M. HENDRICKS

When an eminent humanitarian dies, his life has been so filled with good deeds that they should be brought to the attention of the world so that present and future generations may continue to profit from them. Charles M. Hendricks lived so as to continuously enrich the lives of all who met him and all who became familiar with his work. He was born on a farm near Gratis, Ohio, on December 5, 1878.

His early school days were spent in the traditional "little red brick school house" in the country. He attended high school in Gratis and was class valedictorian. While at Miami University, Oxford, Ohio, he was initiated into Phi Delta Theta fraternity and was captain of the football team. After graduating from Miami he entered the University of Cincinnati where he was on the football team. There he received the degree of doctor of medicine in 1905. Soon he married Edith Louise Dugnid, Toledo, Ohio, who was also a graduate of the University of Cincinnati. Shortly after their marriage they moved to Denver where Dr. Hendricks was interne at the National Jewish Hospital for Tuberculosis. The following year he was assistant physician at the Agnes Memorial Sanatorium in Denver.

In 1907 he accepted the medical directorship of the Albert Baldwin Sanatorium in El Paso, Texas. There he also founded the Hendricks-Laws Sanatorium. He organized El Paso's first tuberculosis clinic in 1909. He employed the most modern diagnostic and therapeutic procedures of the time, being among the first in this country to use artificial pneumothorax bilaterally. Throughout the remainder of his life, he kept abreast of new developments in diseases of the chest around the world and promptly adopted in his own practice those of proved value. In order to have first hand information, he contacted workers in his field at every opportunity. He went to nations, such as England, France and Italy for postgraduate work.

Dr. Hendricks was long an active member of his State Medical Association and was chairman of its committee on tuberculosis for many years. As an activity of this committee he sponsored a plan to place all state hospitals under a state hospital board instead of the board of control.

He became a firm supporter of adequate examination for tuberculosis of all patients admitted to hospitals as well as hospital personnel. In fact he carefully determined the costs on such programs for all hospitals. His program is now becoming generally accepted throughout the state of Texas. He devoted much time to a program for adequate training of nurses in tuberculosis and was insis-

tent that all persons serving as nurses in institutions for the tuberculous be well trained in their profession.

Dr. Hendricks played an active role in the Texas Tuberculosis and Health Association. He was a member of the Board of Directors from 1944 to 1951 and a member of the Executive Committee from 1947 to 1951. While on the Executive Committee, he instituted joint quarterly meetings between that committee and the Tuberculosis Committee of the Texas Medical Association. These joint committees devoted much time and thought and gave leadership in an aggressive program to improve patient care in state supported tuberculosis hospitals. He resigned from the Board of Directors of the Texas Tuberculosis Association because of ill health in 1951. A resolution adopted by the Board of Directors of the Texas Tuberculosis Association at its first meeting following Dr. Hendricks death contains the following: "For many years Dr. Hendricks was a leader in the tuberculosis control program in Texas and in the whole nation. He served well with credit and distinction on the Board of Directors of the Texas Tuberculosis Association. There his counsel and guidance are now sorely missed." He was a member of the National Tuberculosis Association and was a past president of the El Paso County Medical Society, a Fellow of the American Medical Association, honorary life member of the Pan-American Medical Association and a member of the United States Committee of the World Medical Association.

When Murray Kornfeld, in the early 1930's presented a plan to effect an organization of physicians especially qualified in diseases of the chest, Dr. Hendricks saw the potentialities for medical education and research. Inasmuch as no organization in this field was holding regular meetings and promoting programs in local, state, and national medical associations, it appeared that this niche should be filled. He was so enthusiastic about the possibilities that he immediately began to devote an immense amount of time to aid in the promotion of such an organization.

Dr. Hendricks later considered that his greatest achievement in medical organization was his participation in the founding of the American College of Chest Physicians on August 10, 1935. More than any other physician, he fathered this organization from an initial membership of 35 until at the time of his death it had grown to an international body with over 4,500 members in 77 countries and territories. Several months prior to the founding of the American College of Chest Physicians, Dr. Hendricks accepted the editorship of *Diseases of the Chest*, which later became the official publication of the College.

In 1937 he resigned as editor of *Diseases of the Chest* and recommended that he be succeeded by Dr. Frank Walton Burge, Philadelphia, Pennsylvania. However, Dr. Hendricks remained an important member of the editorial board, and throughout the remaining years he continued to contribute significantly to the success of the journal.

In 1946-47 he served as president of the College, and in 1948 he was voted its medal and certificate of award for meritorious achievement in the specialty of diseases of the chest. This is the highest honor that the organization can bestow upon one of its members. In presenting this award, Dr. E. W. Hayes, Monrovia, California, said: "Perhaps more than anyone else Dr. Hendricks has brought the specialty of diseases of the chest, in a comparatively few years, to its present high standing in the profession." In 1953 the Texas Chapter of the American College of Chest Physicians voted to establish an annual lecture to be known as the "Charles M. Hendricks Lecture". The first lecture will be presented this year in San Antonio.

Throughout his career he made notable research contributions and strongly advocated and supported research in various phases of diseases of the chest at every opportunity. In fact he lead the campaign through which the Research and Education Foundation for Diseases of the Chest was established in 1949.

He had long recognized the common cold as the leading cause of absenteeism in America and was firmly convinced that extensive and well coordinated research

conducted in various centers especially equipped for certain phases of the work would ultimately lead to the solution of this health problem. The Research and Education Foundation was organized for this specific purpose. This resulted in the establishment of the Common Cold Foundation to which he was elected executive director. He was so fired with a desire to defeat the common cold that despite failing health he threw all possible energy into this campaign. In fact he dictated promotional letters the day before his death.

It was Charles Hendricks who spearheaded the movement to establish a section on diseases of the chest of the American Medical Association. This was accomplished in 1948.

In addition to being one of America's outstanding physicians, Dr. Hendricks promptly volunteered for duty in the service of his country in World War I. He attained the rank of Lieutenant-Colonel and was an instructor in the poison gas offensive and defensive operation in the inter-service school in Paris. He was promoted to Colonel in the medical reserve and served as commanding officer of the 315th medical regiment from 1922 to 1941.

His activities with the American Red Cross were outstanding. He was chairman of the El Paso chapter for many years, initiated first aid stations in El Paso and other counties, and personally trained the Women's Motor Corps during World War II.

He promoted athletics at every opportunity. He was a member of the Athletic Council of Texas College of Mines, now Texas Western College and personally provided medical care for all athletes. He raised a fund to augment salaries of coaches. His "particular pet" was the Sun Bowl. In 1935 it was decided that El Paso should have a New Year day game between outstanding high school squads. The plan was promoted by the Kiwanis Club. Dr. Hendricks attended the first game, having won two free tickets by submitting the winning name, Sun Bowl, for the game. Since 1935, this has been an annual event. He later conceived the plan of college teams playing this yearly game to be augmented by a spectacular parade and other features. For 10 years Dr. Hendricks was director-general and prime mover of the El Paso Sun Carnival. He mapped all plans, program, festivities, and originated the themes for the Sun Parade of which he was Grand Marshall in 1952.

The Sun Carnival established a Dr. C. M. Hendricks Award to be given to the most outstanding player at the annual New Year football game. The first to be granted was on New Year's Day, 1954, to Dick Shinaut, of Texas Western College. The competing team was that of Mississippi Southern College.

In 1951 Dr. Hendricks was awarded the golden legion certificate of Phi Delta Theta social fraternity. This award signified 50 years of membership. He was a charter member of Rotary and an honorary member of the El Paso Kiwanis clubs and held membership in the American Legion, Veterans of Foreign Wars and Sons of the American Revolution. He had been a director of the El Paso Chamber of Commerce.

Although it was obvious that his health was failing for the past few years he never complained but continued to use all available energy to inspire others and to promote activities to relieve people everywhere of suffering and untimely death. On September 19, 1953 I received a letter devoted to his sincere desire to have the medical organizations dearest to his heart perpetuated and advanced for the good of humanity. He wrote: "As you no doubt know I am quite ill and as I lie here, I felt I wanted you to know how much I prize your friendship. I hope you will continue in good health and carry on." This was the only reference to himself and was the first time he had mentioned his health to me. On December 9, 1953 he died peacefully as he slept.

Throughout the 48 years of their married life Mrs. Hendricks steadfastly aided and supported Dr. Hendricks in all his activities. They reared four daughters, now Mrs. G. N. Broderson, Jr., El Paso; Mrs. C. H. Caldwell, Dallas; Mrs. J. M.

Campbell, Burbank, California; and Mrs. D. B. Thurman, Havana, Cuba, who speak and write of Dr. Hendricks as a most wonderful and beloved husband and father.

To know Charles Hendricks was to love and admire him. He was the acme of goodness. He was calm, deliberate, modest and sincere but always manifested the courage of his convictions. While discussing controversial subjects he never raised his voice but rarely failed to get over his point.

His friendship and encouragement to thousands of physicians, his kindly spirit and helpfulness to other thousands of persons made him one of America's outstanding citizens. His great goodness will continue in the lives of others to whom he so freely imparted his vast store of knowledge.

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CALENDAR OF EVENTS

NATIONAL AND INTERNATIONAL MEETINGS

20th Annual Meeting, American College of Chest Physicians
Fairmont Hotel, San Francisco, June 17-20, 1954.

Third International Congress on Diseases of the Chest
Council on International Affairs
American College of Chest Physicians
Barcelona, Spain, October 4-8, 1954.

CHAPTER MEETINGS

Texas Chapter, San Antonio, May 2.
Georgia Chapter, Macon, May 2.
Kansas Chapter, Topeka, May 4.
California Chapter, Los Angeles, May 8.
Oklahoma Chapter, Oklahoma City, May 9.
New York Chapter, New York City, May 13-14.
New England Chapter, Boston, May 19.
New Jersey Chapter, Atlantic City, May 19.
Illinois Chapter, Chicago, May 20.

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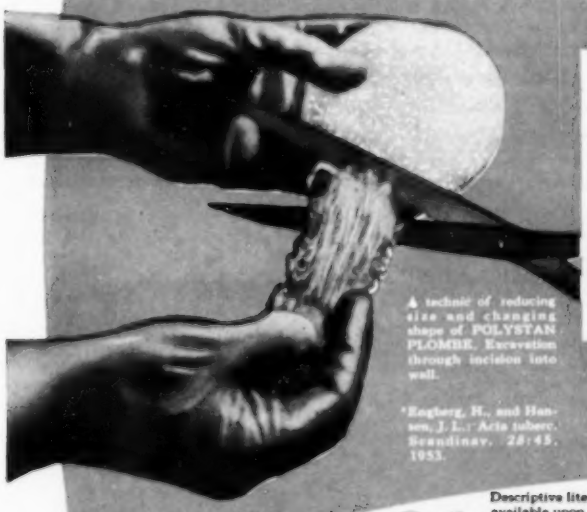

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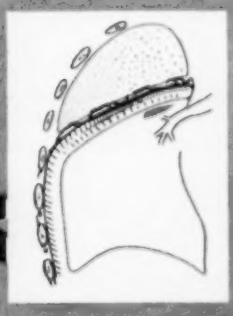
*Engberg, H., and Hansen, J. L.: Acta tuberc. Scandinav. 28:45, 1953.



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Berkstein, E., and Johnson, M.: Streptomycin and Oxytetracycline (Terramycin) in the Treatment of Pulmonary Tuberculosis. Am. Rev. Tuberc. 69:35 (Jan.) 1954.

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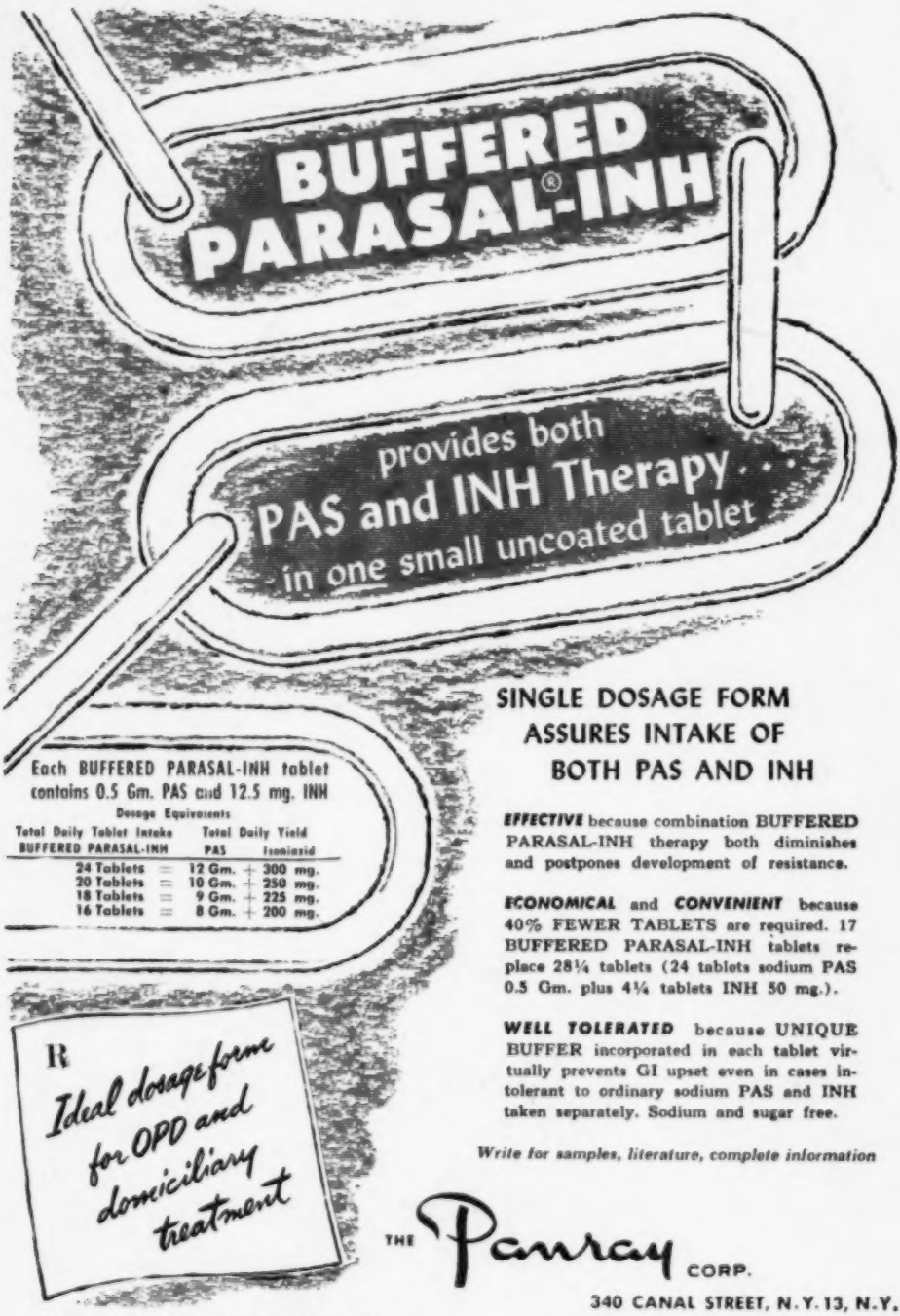

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